Official Title:	**A Single-arm, Prospective Study of Remestemcel-L, Ex-vivo Cultured Adult Human Mesenchymal Stem Cells, for the Treatment of Pediatric Patients who Have Failed to Respond to Steroid Treatment for acute GVHD**
NCT Number:	NCT02336230
Document Date:	Protocol Version 7.0: 18 December 2017 SAP Version 5.0: 08 February 2018

A Single-arm, Prospective Study of Remestemcel-L, *Ex-vivo* Cultured Adult Human Mesenchymal Stromal Cells, for the Treatment of Pediatric Patients who Have Failed to Respond to Steroid Treatment for Acute GVHD

STUDY PROTOCOL

Protocol Number MSB-GVHD001
Clinical Development Phase 3
Protocol Version 7.0
Protocol Date: 18 December 2017

Sponsor: Mesoblast International Sàrl (Mesoblast)
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Confidentiality Statement

INVESTIGATOR'S SIGNATURE

Study Title: A Single-arm, Prospective Study of Remestemcel-L, *Ex-vivo* Cultured Adult Human Mesenchymal Stromal Cells for the Treatment of Pediatric Patients who Have Failed to Respond to Steroid Treatment for Acute GVHD

I have read and understood the contents of this protocol and the Investigator's Brochure and agree to conduct this study in compliance with the protocol, Good Clinical Practice, and other applicable regulatory requirements.

I accept the oversight of the study monitor designated by Mesoblast and the control procedures, including verification by access to source documents, as required by the study monitoring and audit functions of Mesoblast or its designee and the audit functions of regulatory agencies in accordance with Good Clinical Practice.

I understand that any changes to this protocol not associated with procedures necessary for the safety of subjects that are instituted by the Investigator without previous discussion with the Mesoblast Medical Director or designee would constitute a violation of the protocol.

I agree that the investigational agents supplied by Mesoblast will be used solely for the purpose of conducting this investigation.

I will personally conduct the investigation as described herein and in the Mesoblast Clinical Research Agreement.

Agreement Signature:

Principal Investigator (Please print)	Principal Investigator (Signature)	Date

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PROTOCOL SYNOPSIS

Sponsor Mesoblast International Sàrl	**Study Phase** Phase 3	**Protocol Number** MSB-GVHD001

Investigational Product
Remestemcel-L (*ex-vivo* cultured adult human mesenchymal stromal cells [MSCs] cryopreserved in Plasma-Lyte® A supplemented with human serum albumin (5%) and dimethyl sulfoxide (10%). [redacted]

Protocol Title
A Single-arm, Prospective Study of Remestemcel-L, *Ex-vivo* Cultured Adult Human Mesenchymal Stromal Cells, for the Treatment of Pediatric Patients who Have Failed to Respond to Steroid Treatment for Acute GVHD.

Indication
Remestemcel-L will be evaluated in pediatric subjects with acute Graft versus Host Disease (aGVHD) following allogeneic hematopoietic stromal cell transplant (HSCT) that has failed to respond to treatment with systemic corticosteroid therapy.

Objectives
Primary Objectives:

1. To evaluate the efficacy of remestemcel-L in pediatric subjects with Grades B-D aGVHD who have failed to respond to steroid treatment post allogeneic HSCT.
2. To gather additional information on the safety of remestemcel-L in pediatric subjects with Grades B-D aGVHD that has failed to respond to steroid treatment post allogeneic HSCT.

Secondary Objectives:

1. To determine the correlation between response to remestemcel-L at Day 28 and survival at Day 100.
2. To obtain quality of life data on remestemcel-L-treated subjects via the Pediatric Quality of Life Inventory™ (PedsQL™; Appendix 1 and Appendix 2) and the pediatric global health-related quality of life (HRQOL) Parent Proxy Report (Appendix 3).
3. To measure the functional status of remestemcel-L-treated subjects using the Karnofsky/Lansky scale (Appendix 4).

[redacted]

Planned Follow-up Study of Safety and Health Outcomes
Additional safety will be gathered under a separate protocol (MSB-GVHD002), subsequent to the present study, in order to capture health outcomes and safety data out to Day 180.

Study Population
This study will evaluate the efficacy and safety of remestemcel-L in pediatric subjects with aGVHD that has failed to respond only to first-line systemic steroid treatment. The trial will exclude subjects who have received second-line treatment for aGVHD prior to study screening, in order to evaluate remestemcel-L's effects in the absence of other second-line agents. The study plans to treat at least 48 pediatric subjects, male and female, between the ages of 2 months and 17 years inclusive, with acute Graft versus Host Disease (aGVHD) following allogeneic hematopoietic stem cell transplant (HSCT) that has failed to respond to treatment with systemic corticosteroid therapy. Subjects may have Grades C and D aGVHD involving the skin, liver and/or gastrointestinal (GI) tract or Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease.

Acute GVHD Treatment Response Criteria
Complete response (CR)- Resolution of aGVHD in all involved organs
Partial response (PR)- Organ improvement by at least one stage without worsening of any other organ.
Overall response (OR)- Includes both complete response and partial response
Very good partial response (VGPR)- Subset of PR patients: Fulfillment of the CR criteria with the exception of one or more of the following:
Skin: no rash, non-progressive stage 1 rash, or residual erythematous rash involving <25% of the body surface without bullae (not including residual faint erythema or hyperpigmentation);
Liver: resolving elevations of total serum bilirubin concentration or total serum bilirubin concentration of <2 mg/dl or <25% of baseline at enrollment
Gut: minimal gastrointestinal symptoms as described below:
Tolerating food or enteral feeding
Predominantly formed stools
No overt GI bleeding or abdominal cramping
No more than occasional nausea or vomiting
Mixed response (MR)- Improvement in at least one evaluable organ stage with worsening in another
No response (NR)- No change in any organ stage in any organ system and no improvement in organ stage
Progression- Deterioration in at least one organ system by one stage or more with no improvement in any other organ
Responder- Subjects who achieve an overall response (OR)
Non-responder- Subjects who do not achieve an OR.

Efficacy Assessments
Primary Endpoint
The rate of overall response (OR) in the study population at Day 28 post initiation of therapy (Day 0) with remestemcel-L (MSC).

Secondary Endpoints

1. Overall survival at Day 100 post initiation of remestemcel-L therapy
2. Rate of very good partial response (VGPR) at Day 28 post initiation of remestemcel-L therapy
3. Rates of OR and VGPR at Day 100 post initiation of remestemcel-L therapy
4. Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy, stratified by organ involvement
5. Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy, stratified by individual subject organ involvement
6. Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy, stratified by baseline aGVHD grade
7. Overall survival at Day 100 post initiation of remestemcel-L therapy, stratified by baseline aGVHD grade and organ involvement
8. Rate of aGVHD progression requiring additional aGVHD medications/therapy through Day 100 post initiation of remestemcel-L therapy
9. Effect of additional remestemcel-L therapy after Day 28 on rate of OR and VGPR at Days 56 and 100 post initiation of remestemcel-L therapy.

[redacted]

Safety Assessments

Safety endpoints will include:

1. Adverse events
2. Serious adverse events
3. Infusional toxicity
4. Formation of ectopic tissue foci.

Inclusion Criteria

Subjects will be eligible for participation in the study only if they meet ALL of the following criteria:

1. Subject was diagnosed with Grade B-D acute GVHD requiring corticosteroid systemic therapy. The subject may have Grade C or D aGVHD involving the skin, liver, and/or gastrointestinal (GI) tract or may have Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease. Acute GVHD is defined as the presence of skin rash and/or persistent nausea, vomiting, and/or diarrhea and/or cholestasis presenting in a context in which aGVHD is likely to occur and where other etiologies such as drug rash, enteric infection, or hepatotoxic syndromes are unlikely or have been ruled out.

2. Subject is 2 months to 17 years of age, inclusive
3. Subject has failed to respond to steroid treatment, with failure to respond defined as any Grade B-D (IBMTR grading) aGVHD that shows progression within 3 days or no improvement within 7 days of consecutive treatment with 2 mg/kg/day of methylprednisolone or equivalent.
4. Subject must be able to be treated with remestemcel-L within 4 days of signing of informed consent.
5. Subjects who have had persistent GI GVHD, as manifested by diarrhea with stool volume < 500 mL/ day (for subjects >50 kg), or < 30 mL/kg/day (for subjects ≤50 kg). See Table 2: GVHD Organ Severity Criteria for values in ml/m^2. In the absence of nausea or vomiting, subject may still be considered to have Grade B GVHD if
    a. other causes of diarrhea have been ruled out (e.g., C. difficile, adenovirus or cytomegalovirus (CMV) infection, oral magnesium administration)

       and if

    b. the low stool volume reflects the effects of fasting, narcotics, or anti-diarrheal medications.

6. Subject must have adequate renal function, as defined by a calculated creatinine clearance of >30 mL/min per 1.73m^2. For subjects 1 to 18 years of age, creatinine clearance should be calculated using the Bedside Schwartz equation:

   GFR (ml/min per 1.73 m^2) = [0.413 × height (cm)]/Serum creatinine (mg/dl)

   For subjects less than 1 year old, renal function should be determined using the Schwartz equation adjusted for this age group:

   Creatinine clearance (ml/min per1.73 m^2)= (height [cm] x 0.45)/ (serum creatinine [mg/dL])

7. Subject has a minimum Karnofsky/Lansky Performance Level of 30 at the time of study entry
8. Subject (or legal representative where appropriate) must be capable of providing written informed consent.
9. Female subjects of childbearing potential (≥ 10 years of age) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for the follow-up time period. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method. Guidance on childbearing potential and pregnancy testing is located in Appendix 6.

10. Male subjects with partners of childbearing potential must agree to use adequate contraception (barrier method or abstinence) during the study, including the follow-up time period.
11. The subject must be willing and able to comply with study requirements, remain at the clinic, and return to the clinic for the follow-up evaluation, as specified in this protocol during the study period.

Exclusion Criteria

Subjects will not be eligible for participation in the study if they meet ANY of the following criteria:

1. Subject has Grade B aGVHD with skin-only involvement.
2. Subject has received any second line therapy to treat aGVHD prior to screening.
3. Subject has received systemic agents other than steroids and prophylactic agents for primary ***treatment*** of acute GVHD.
4. Subject shows evidence of diffuse alveolar hemorrhage or other active pulmonary disease, which is likely to require more than 2L of oxygen via face mask or an estimated FiO_2 of 28% via other delivery methods in order to sustain an O_2 saturation of 92%.
5. Subject has any underlying or current medical or psychiatric condition that, in the opinion of the Investigator, would interfere with the evaluation of the subject, including but not limited to uncontrolled infection, heart failure, pulmonary hypertension, etc.
6. Subject has received any stem cell agents (other than hematopoietic graft) during study participation or within 30 days prior to study entry. Donor Leukocyte Infusion (DLI) is excluded during study participation or within 30 days prior to study entry. Previous use of irradiated granulocytes within 30 days is permitted.
7. Subject has received an HSCT transplant for a solid tumor disease.
8. Subject has had prior treatment with mesenchymal stromal cells (MSCs), including remestemcel-L.
9. Subject shows evidence of severe (require treatment) hepatic veno-occlusive disease (VOD) or sinusoidal obstruction at screening.
10. Subject has had positive laboratory test results indicating infection with the human immunodeficiency virus (HIV) at any time and/or active hepatitis B or C virus infection within 3 months prior to screening.
11. Subject shows evidence of encephalopathy as defined by a change in mental status since the onset of aGVHD.
12. Subject is a female who is pregnant, lactating, or is planning a pregnancy during study participation, including the follow-up period.
13. Subject is currently being treated for a solid tumor malignancy.
14. Subject has participated in any interventional clinical trial for an aGVHD therapeutic agent. However, in exceptional cases (see Section 7.9.1), experimental agents may be administered to enrolled subjects at the Investigator's discretion.
15. Subject has participated or is currently participating in any autologous or allogeneic stem cell or gene therapy study for the treatment of aGVHD. Patients participating

in investigative protocols aimed at modification of the transplant graft (such as T cell depletion) or aimed at modification of the conditioning regimen will be allowed in the study.

16. Subject has a known hypersensitivity to dimethyl sulfoxide (DMSO) or to porcine or bovine proteins.

Treatment Groups

This is a single-arm study; all enrolled subjects are to be treated with remestemcel-L.

Treatment Plan

The trial design, including treatment plan, is outlined schematically in Figure 1, which follows this synopsis.

Initial Therapy

Subjects will be treated with intravenous (IV) remestemcel-L at a dose of 2 x 10^6 MSC/kg (actual body weight at screening) twice per week for each of 4 consecutive weeks. Infusions will be administered at least 3 days apart and no more than 5 days apart for any infusion. All 8 infusions must be administered by Day 28 ± 2 days.

Subjects may continue to be treated with a stable dose of systemic steroid therapy until they are eligible for steroid taper and may continue on an established regimen of baseline prophylactic therapy following initiation of remestemcel-L (Day 0). No other medications for the treatment of aGVHD are to be introduced to subjects during the initial 28 days post remestemcel-L administration unless disease progression, as defined below, has occurred. Addition of other secondary line agents prior to Day 28 would constitute failure to respond, in which case, the treated subject would remain on the study for safety follow up.

Any changes in baseline prophylaxis regimen should be recorded in the eCRF and reason for change in regimen should be discussed with the Medical Monitor. Changes in dose or prophylactic agent due to administration route intolerance or toxicities are allowed at the discretion of the investigator with prior approval from the Medical Monitor as these changes could be confused as second-line therapies.

Steroid taper

If improvement in GVHD, as defined by OR, is observed for a period of 3-5 days and after at least two doses of remestemcel-L, the dosing of methylprednisolone or equivalent may be tapered. A steroid taper rate of at least 10% of the dose per week, not exceeding 25% of the dose per week, is recommended as described in Appendix 5, with the goal of discontinuing steroid by 10 weeks after initiating taper.

Assessments

GVHD assessments will be performed at screening and weekly, beginning on Day 14, until Day 100 (±7 days)/End of Study. Assessments must be after the 2nd dose of remestemcel-L is administered for each assessment week of the Initial Therapy period (or after the 1st dose of remestemcel-L during Continued Therapy). The weekly assessment visits should be

conducted at least 24 hours after the most recent remestemcel -L infusion. Weekly GVHD assessments will be used to determine whether the subject's GVHD status has progressed from baseline assessment (through Day 28), according to the definition of *progression of disease*, below. From Day 28 to Day 100, weekly GVHD assessments will be compared to the most recent prior assessment to determine whether the subject's GVHD status has progressed. Rescue therapy may be administered if necessary. If new GVHD medications are administered as rescue therapy based on these assessment(s), no further remestemcel-L infusions will be allowed. Subjects would remain in the study regardless of response and would continue to be evaluated per the assessment schedule.

Progression of disease is defined as increase by one or more grade from screening/baseline assessment up to Day 28 and as increase by one or more grade from the most recent prior assessment from Day 28 to Day 100. Progression is not defined as 'mixed response' according to the definitions described above under **Acute GVHD Treatment Response Criteria**.

Day 28 Therapy Assessment:
A therapy assessment will be performed on Day 28 (±2 days) to determine treatment response and whether a subject will be provided continued therapy. The Day 28 therapy assessment must be at least 24 hours after the last dose of remestemcel-L is administered. Continued Therapy will be allowed for subjects according to their response to treatment, as described below.

Day 56 Assessment of Response to Continued Therapy
A therapy assessment will be performed on Day 56 (±2 days) from treatment initiation for subjects receiving Continued Therapy after Day 28, in order to determine treatment response to the Continued Therapy. The Day 56 therapy assessment must be at least 24 hours after the last administration of remestemcel-L.

Continued Therapy
Eligible subjects may receive an additional 4 once-weekly infusions of remestemcel-L at the same initial dose of 2 x 10^6 MSC/kg actual body weight at screening, which would begin within one week after the Day 28 therapy assessment. Infusions will be given once weekly (± 2 days) and all infusions must be administered within 28 days (± 2 days) from the first infusion. No additional treatment with remestemcel-L is allowed at any other point in time unless the criterion for GVHD flare, as defined in this protocol, is met.

Eligibility for Continued Therapy
Eligibility to receive Continued Therapy after the initial 4-week treatment period is dependent upon the results of the subject's response assessments at Day 28, as defined in Table 4, compared with baseline, as follows:

Complete Response (CR): If a subject displays CR, then no additional remestemcel-L will be administered.

No Response (NR): If a subject displays NR, then no additional remestemcel-L will be administered.

Partial Response (PR): If a subject displays PR, the subject will receive Continued Therapy.

Mixed Response (MR): If a subject displays MR, the subject will receive Continued Therapy.

GVHD flare: Subjects who have a GVHD flare of Grade B-D, after achieving a CR and before Day 70 post treatment initiation, may receive additional remestemcel-L treatment per the Initial Therapy plan, consisting of remestemcel-L, IV, at a dose of 2 x 10^6 MSC/kg actual body weight at screening, twice per week for each of 4 consecutive weeks. GVHD flare is defined as any increase in aGVHD symptoms (measured by GVHD grade B-D) beyond 28 days post first infusion, subsequent to achieving CR to Initial Therapy, or beyond Day 56 after achieving CR to Continued Therapy. If a subject has begun other second line GVHD therapy, they would *not* be eligible to receive additional remestemcel-L treatment. Subjects are eligible for a single treatment for flare.

Other GVHD therapy
If a subject begins other second-line GVHD therapy within the period of Initial and Continued Therapy (through Day 56, if applicable), he or she would be considered to have failed treatment and would be ineligible to receive any further remestemcel-L therapy upon receiving the other second-line GVHD therapy.

Route of Administration and Dose
Remestemcel-L (ex-vivo cultured adult human MSCs) will be administered intravenously at a dose of 2 x10^6 MSC /kg of actual body weight at screening. Remestemcel-L is stored and distributed in cryogenic bags and cryogenic vials.

Duration of Treatment
Enrolled subjects will receive Initial Therapy for 4 weeks; eligible subjects will receive Continued Therapy for an additional four weeks, beginning within one week after the end of Initial Therapy period. Subjects may receive Flare Therapy for an additional four weeks if flare criteria is met.

Duration of Study
Subjects may receive treatment for up to 8 weeks and will be followed out to 100 ± 7 days. Total duration of study participation per subject is up to 111 days to account for the 4-day screening window and End of Study visit ±7 days.

An extension study under a separate protocol (MSB- GVHD002), subsequent to the present study, is being conducted in order to capture health outcomes and safety data out to Day 180.

Statistical Analysis

Sample Size

The primary objective of this trial is to confirm efficacy of remestemcel-L in improving Day 28 OR rate within the efficacy population. For assessment of efficacy, an effect size of 20%, which has been deemed clinically meaningful based on discussions with clinical experts on aGVHD, was used to calculate the null hypothesis. The null hypothesis was calculated using 45% OR, a rate that is 20-points lower than the anticipated 65% OR rate to remestemcel-L. This estimated 45% response rate is supported by data showing comparable Day 28 OR rates for historical populations of aGVHD patients treated with standard of care, which varies across institutions, but generally consists of treatment with immune-suppressive agents used serially or in combination. Sample size was determined using a normal approximation to the binomial distribution under the assumption of a two-sided test of significance level 5% for a single proportion and a difference in proportion of 20%. This is equivalent to one-sided testing at 2.5% of the null hypothesis that the Day 28 OR rate is at most, 45%, versus the alternative hypothesis that the Day 28 OR rate is 65% or greater. The minimum sample size required to meet the primary objective with 80% power is 48 for the FAS population. At least 48 subjects will be enrolled. In order to account for dropouts/missing data and to ensure that this study has sufficient power, an additional increased enrollment of up to 10% of the minimum required enrollment (48) is planned.

Statistical Methods

Analysis Populations

As this is a single arm study, the evaluable population for efficacy will be considered the *full analysis set* (FAS), which will include all subjects who provided informed consent, were screened and found eligible to enter the study. The *modified full analysis set (mFAS)* is the same as the FAS, but only for patients treated with IMP in cryogenic vials. The primary and secondary efficacy analyses will be performed on the FAS population. The *per-protocol* (PP) population will include all subjects from the FAS population who had no major protocol violations during the study. The primary and secondary efficacy analyses performed on the mFAS and PP populations will be considered supportive. The *safety population* will include all subjects who have signed the informed consent form and have received at least one dose of study drug. We may conduct sensitivity analyses comparing results from patients treated with product in vials to results for all patients for each of the analysis populations.

General Statistical Considerations:

Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Two-sided confidence intervals at the 95% level will

be presented for estimates of proportions. All statistical tests will be two-sided at the alpha<0.05 level of significance, unless otherwise noted.

The primary and secondary analyses will be based on the FAS population. Primary and secondary analyses performed on the mFAS and PP populations will be considered supportive. Analyses of the PP populations will be used to assess sensitivity and thus will be considered supportive.

Pre-treatment demographics and subject characteristics will be summarized. Time from HSCT to onset of aGVHD and from onset of aGVHD to initiation of study drug will be summarized. Involvement of the skin, lower gastrointestinal (GI) tract, and liver will be summarized by the number of subjects with one organ, two organs, or all three organs involved at baseline.

Efficacy Analyses
OR at Day 28 as response to remestemcel-L treatment is the primary efficacy endpoint. Missing data for the primary endpoint will be considered as non-responders. Details on imputation will be specified in the Statistical Analysis Plan (SAP) prior to database lock. A hypothesis test will be performed to assess whether the percentage of responders is statistically significantly different from the control percentage of 45% used to calculate the null hypothesis.

Survival will be assessed from initial remestemcel-L treatment to the last date of assessment. The association between Day 28 OR and survival at Day 100, and between Day 28 VGPR and survival at Day 100, will be tested for statistical significance. First, the associations will be tested using a Cochran-Mantel-Haenszel (CMH) test stratifying by baseline aGVHD grade. Day 100 survival Kaplan-Meier curves will be plotted by Day 28 responder and non-responder groups, and differences between these groups will be tested for a statistically significant difference using the log-rank test. The odds ratio for survival at Day 100 given responder status at Day 28 will be presented and tested for statistical significance (whether statistically significantly greater than 1).

Additional secondary endpoints will be evaluated. The rate of VGPR will be described. The number and proportion of VGPR responders, non-responders, and missing values, at Day 28, Day 56, and at Day 100 will be summarized. The rates of OR and VGPR at Day 28, Day 56, and at Day 100 will be reported by skin, gut (lower GI), or liver involvement at baseline. The rates of OR and VGPR will also be reported by the mutually exclusive Skin-only and "Not skin-only" categories. The number and percentage of responders at each time point and for each endpoint will be summarized by baseline GVHD grade. The number and percentage of survivors at Day 100 from first infusion date will be summarized by baseline grade and organ involvement. The incidence rate of GVHD progression requiring additional GVHD medications or therapy will be summarized by number and proportion of subjects. Side-by-side shift tables for response at Day 56 and response at

Day 100, versus response at Day 28, summarizing the effect of additional IMP therapy, will be presented.

Efficacy analyses will include a summary of aGVHD grade at baseline, Day 28, Day 56 and Day 100. Shift tables in aGVHD organ stages from baseline to Day 28 will be presented. Shift tables for organ stages will also be presented by organ involvement. In addition, shift tables will be presented for skin-only stages and separately for "All Others" (that is, excluding skin-only). Response by organ for each of these groups (by individual organ involvement, skin-only and all-others) will be summarized as improving, stable or progressing, together with the number of deaths in each case.

As sensitivity analyses, survival will also be calculated from the date of transplant and from the date of diagnosis of aGVHD to the last date of contact. For all survival data, Kaplan-Meier survival curves will be generated and relevant subgroups will be compared using the log-rank test. Kaplan-Meier curves will also be generated by number of organs involved, and categorized by number of infusions.

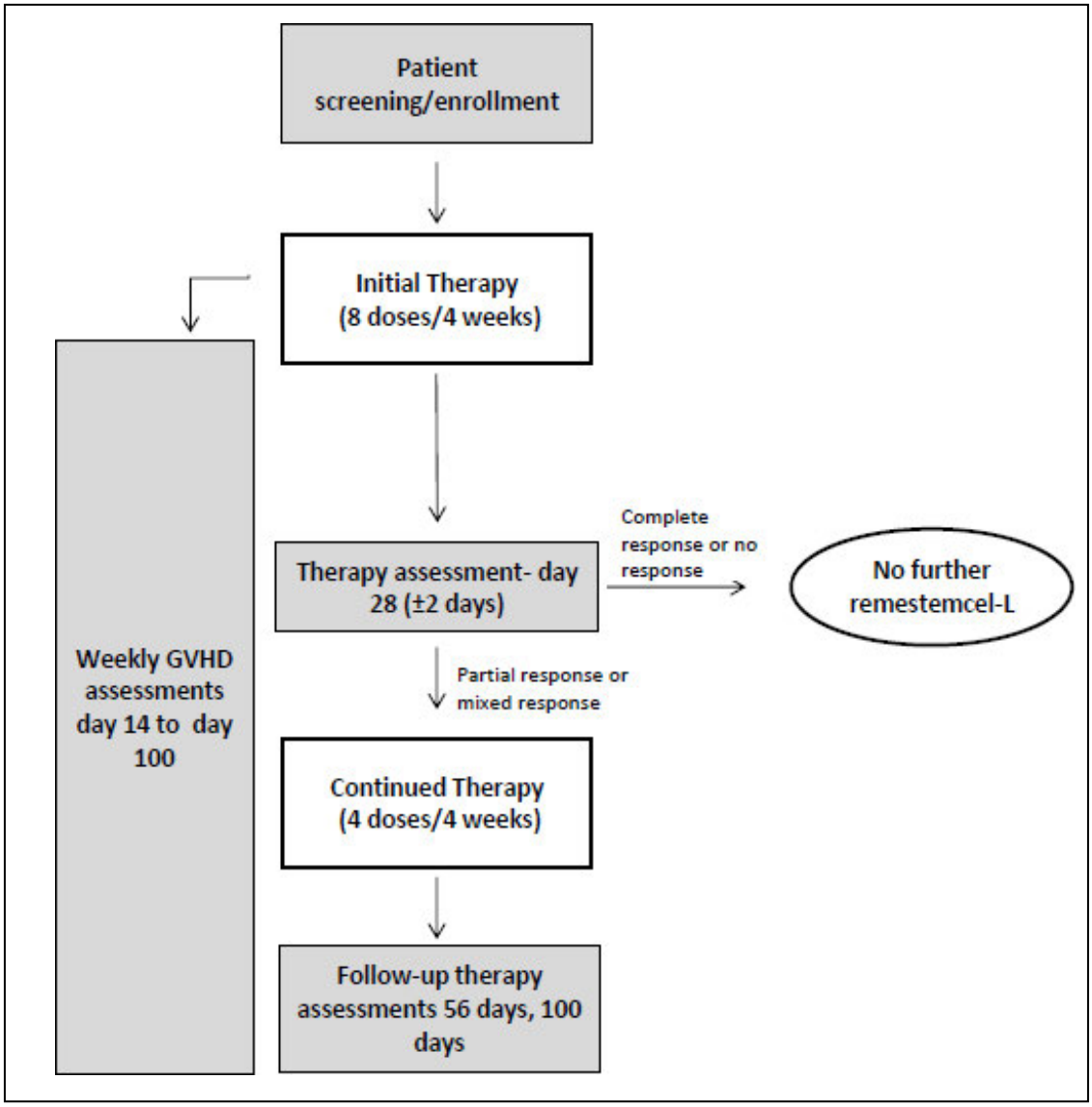
Effect of continuing therapy beyond Day 28 will be tabulated by number of infusions (less than 8 and greater than 8) and by baseline aGVHD grade in shift tables of response status (i.e. OR, VGPR, etc.) at Day 28, Day 56 and Day 100.

[redacted]

Safety Analyses
Safety assessments will be summarized with descriptive statistics for subjects in the safety population as described below. Listings will be provided for all adverse events (AEs). Vital signs will be provided as change from baseline tables by infusion number categories.

Interim Analysis	One interim analysis for futility is planned for this study. The interim analysis for futility will be conducted after approximately 30 subjects have been treated with IMP and have completed treatment through 28 days (or have discontinued early or died). Details of this analysis are discussed in the Statistical Analysis Plan (SAP) for the study and in the DSMB charter.

Figure 1: Schematic Diagram of the MSB-GVHD001 Trial Design



[†]Subjects who have a GVHD flare of Grade B-D after achieving a complete response (CR) at Day 28 (following Initial therapy) or Day 56 (following Continued Therapy) and before Day 70 may receive additional remestemcel-L treatment per the Initial Therapy plan.

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GLOSSARY OF ABBREVIATIONS

ACI	Acute Cardiac Infarct Study
ACR	Albumin-to-creatinine ratio
ADA	American Diabetes Association
AE	Adverse event
aGVHD	Acute Graft versus Host Disease
ALT [SGPT]	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST [SGOT]	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatine kinase
CMV	Cytomegalovirus
CMH	Cochran-Mantel-Haenszel
CPK	Creatine phosphokinase
CR	Complete Response
CRF	Case report form
CRT	Cardiac Resynchronization Therapy
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DAS28	Disease Activity Score in 28 Joints
DBP	Diastolic blood pressure
DCS	Data collection specification
DLCO	Diffusing capacity for carbon monoxide
DLI	Donor Leukocyte Infusion
DMC	Data Monitoring Committee
DMSO	Dimethyl sulfoxide
DSMB	Data Safety Monitoring Board
EAC	Events Adjudication Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
EDC	Electronic data capture
EEA	European Economic Area
EOT	End of Treatment
eGFR	Estimated glomerular filtration rate
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
FiO2	Fractional inspired oxygen concentration

GLOSSARY OF ABBREVIATIONS

GFP	Green fluorescence protein
GI	Gastrointestinal
γ-GT	Gamma-glutamyl transpeptidase
GCP	Good clinical practice
GMP	Good Manufacturing Practice
GFR	Glomerular filtration rate
GVHD	Graft versus Host Disease
GGT	Gamma-glutamyl transpeptidase
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
Hct	Hematocrit
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLT	High Level Term
hMSC	Human mesenchymal stem cells
HR	Heart Rate
hsCRP	High sensitivity C-reactive protein
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
IBMTR	International Bone Marrow Transplant Registry
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational New Drug
INN	International Non-Proprietary Name
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
MA	Medical advisor
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mFAS	Modified full analysis set
MLR	Mixed lymphocyte reaction
MPC	Mesenchymal precursor cells
MPV	Mean platelet volume

GLOSSARY OF ABBREVIATIONS

MDRD	Modification of Diet in Renal Disease
mITT	Modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MR	Mixed Response
MSC	Mesenchymal stromal cells
MTX	Methotrexate
NR	No Response
NIH	National Institutes of Health
NSAID	Non-Steroidal Anti-inflammatory Drugs
NYHA	New York Heart Association
O2	Oxygen
OR	Overall Response
PedsQL™	Pediatric Quality of Life Inventory™
PFT	Pulmonary Function Testing
PP	Per-protocol population
PR	Partial Response
PRA	Panel reactive antibody
PT	Preferred Term
PT/INR	Prothrombin time/International normalized ratio
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
QLS	Quintiles Lifecycle Safety
RBC	Red blood cell
RDW	Red cell distribution width
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard Error of Mean
SMBG	Self-monitored blood glucose
SMT	Study Management Team
SPC	Summary of Product Characteristics
SOC	System Organ Class
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
TG	Triglycerides
TNF-α	Tumor necrosis factor-α
ULN	Upper limit of normal
VGPR	Very Good Partial Response
VOD	Veno-occlusive disease
v/v	Volume/volume
WBC	White blood cell

1. BACKGROUND

1.1 Acute Graft-versus Host Disease

Graft versus host disease (GVHD) is a progressive and lethal complication of hematopoietic stem cell transplantation (HSCT) and donor leukocyte infusion. Two clinically distinct forms of GVHD have been described, consisting of acute GVHD, which typically occurs within 100 days of HSCT, [1] and chronic GVHD, which is characterized by later onset.[2] However, this arbitrary temporal distinction between the acute and chronic forms of GVHD has been largely discarded with the recognition of these forms as discrete pathophysiologic conditions definable by separate clinical and diagnostic criteria. [3,4]

Occurrence of acute GVHD (aGVHD) after allogeneic transplantation is fairly common, with Grades II to IV aGVHD reported in approximately 39% of cases involving sibling donors and 59% of cases with unrelated donors.[5] Overall, an estimated 20% to 80% of patients who receive allogeneic HSCT develop acute GVHD, even after prophylaxis with immunosuppressive agents. [6]

While aGVHD is common among patients with allogeneic transplantation, overall, it is a rare disease, affecting about 10,000 individuals per year worldwide, with an estimated 2,000 cases found in children (Table 1). Approximately 5,500 of worldwide aGVHD cases are refractory to steroid, [4] 1,000-1,200 of which are pediatric cases.

Table 1: Worldwide Incidence of Steroid Refractory aGVHD

	All Patients	Pediatric (<18 years)
Allogeneic HSCT	25,000	5,000
aGVHD Requiring systemic treatment (Grades B-D)	10,000	2,000
Refractory aGVHD	5,000-6,000	1,000-1,200

Source: CIBMTR Research Analysis.

In aGvHD, alloreactive T cells present in the donor cell transplant recognize the recipient's tissues as foreign and mount an immunological attack, causing inflammation and tissue damage primarily affecting the gastrointestinal (GI) tract, skin, and liver. [7] Human leukocyte antigen (HLA) disparity between HSC donor and recipient is the key driver of GVHD, causing donor T cells to recognize recipient tissue as foreign. [7] The severity of the disease is associated with the degree of HLA mismatch between the donor and the recipient, and a greater mismatch will result in more aggressive alloreactivity. [8] Damage to recipient tissue caused by the HSCT conditioning regimen (irradiation or chemo-ablation) creates a cellular and molecular

environment that is conducive to GVHD. The tissue damage leads to the increased secretion of proinflammatory cytokines, which promote donor T cell proliferation and differentiation and interaction with recipient antigen presenting cells. Alloreactive donor T cells traffic to target tissues (skin, gut, liver) and release soluble mediators that mediate cytotoxicity and end organ damage. Other donor immune cells, including natural killer cells, neutrophils and monocytes, are also activated and recruited to target organs and contribute to host tissue destruction. [9] This adverse immune reaction increases over time as the expanding tissue damage mediated by alloreactive immune cells leads to more cytokine production. A vicious cycle ensues: amplification of cytokine expression supports further proliferation and activation of alloreactive immune cells, which in turn leads to further tissue damage. [7]

Consequently, aGVHD potentially involves multiple organ systems, with varying degrees of clinical severity.

Acute GVHD onset primarily affects the skin, the liver, and the gastrointestinal (GI) tract, though the GVHD reaction targets a number of different host cells, including those of the skin epithelia and mucosa, hair follicles, intestinal crypts, liver bile ducts, bone marrow, and immune system. [1,7] Disease onset often manifests clinically as a pruritic maculopapular rash that first appears on the nape of the neck, shoulders, ears, palms of the hands, and soles of the feet. The liver is the next most commonly affected organ after skin; symptoms of liver involvement include jaundice and increased alkaline phosphatase levels that indicate damage to the bile canaliculi and portend cholestasis. The GI tract is the third organ among the tissues most commonly affected in acute GVHD, frequently presenting as nausea, vomiting, intestinal bleeding, cramping, and diarrhea. GI involvement is often the most severe of the organs affected and can be the most difficult to treat. The large volumes of watery diarrhea common to intestinal involvement in acute GVHD often transitions into bloody diarrhea that prompt the need for frequent transfusions. [7]

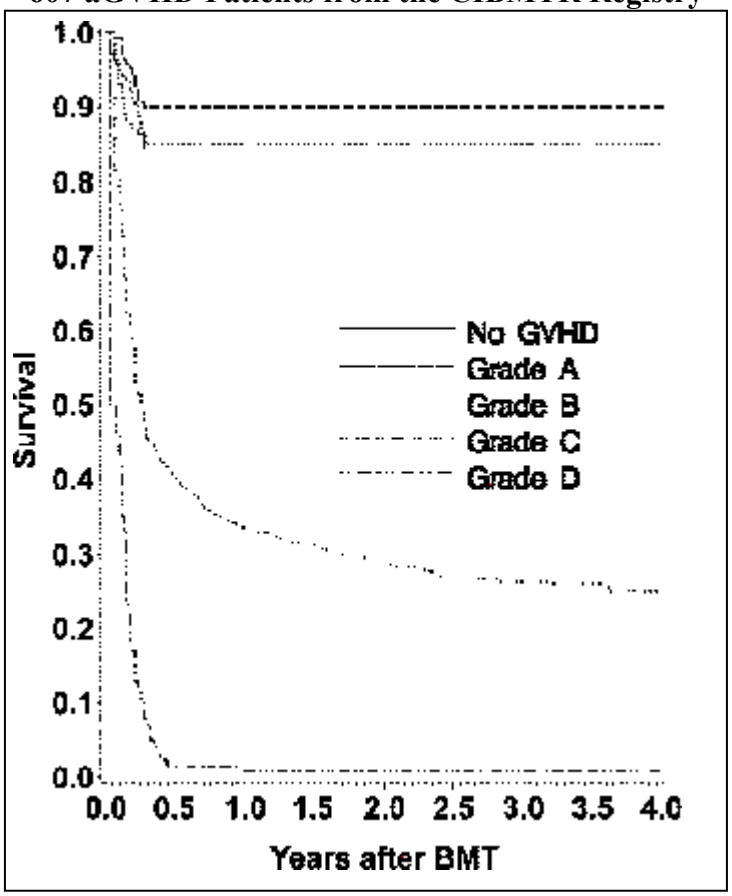
1.2 Current Treatment of aGVHD and Prognosis

Presently, there are no FDA-approved therapies for treatment of steroid-refractory aGVHD. Available treatment options to prevent aGVHD have historically involved front-line therapy with glucocorticoids along with different combinations of prophylaxis agents such as methotrexate and cyclosporine A. [6,10-12] While many patients who develop aGVHD respond well to first-line corticosteroid treatment, steroids achieve complete response rates in only approximately 50% of cases. [13] Many aGVHD patients display inadequate response to corticosteroid, with

approximately 10% to 30% of aGVHD patients progressing to the more severe Glucksberg Grades III or IV GVHD.[5]

As shown by the survival curves in Figure 2, the prognosis for patients with the most severe forms of aGVHD (IBMTR Grades C and D) is dismal, primarily because of greater risk for infectious complications, immunosuppression- mediated toxicity, and often incomplete GVHD remission. [14] Patients that do not respond to steroid therapy have expected one-year survival rates of just 5% to 30%. [6,8,15-19] A wide variety of second-line immunosuppressive agents are commonly used to treat steroid-refractory aGVHD (SR-aGVHD), though there is little evidence to support the efficacy of these drugs as secondary therapy for aGVHD. [6]

Figure 2: Probability of Survival According to Maximum GVHD Grade for a Sampling of 607 aGVHD Patients from the CIBMTR Registry



1.3 Grading of Acute GVHD

Acute GVHD is a heterogeneous set of disease processes that potentially involves multiple organ systems, with varying degrees of severity by organ system. Disease onset typically manifests most commonly in the skin, with the GI tract and liver as the next most common sites involved. [17] Historically, classification systems of aGVHD have been established to segregate aGVHD according to severity. The severity grade of aGVHD has been shown to correspond to overall survival, with increased transplant-related mortality correlating with higher aGVHD grade. [20] One of the first grading systems, published by Glucksberg and colleagues in 1974, [21] involves assigning a stage of 1 to 4 to each involved organ, as described in Table 2, and combining these stages to yield an overall grade ranging from I to IV (Table 3).

Another grading system, which will be used in the present study, was devised by the International Bone Marrow Transplant Registry (IBMTR) and classifies aGVHD severity on a scale of A to D. While a modified Glucksberg grading system is recommended in the most current published consensus statement for diagnosis and management of aGVHD, [12] the current study will use the IBMTR classification system in order to maintain consistency with previous studies of remestemcel-L for aGVHD. Table 3 presents a summary of the IBMTR compared with the IBMTR grading systems for GVHD. [22]

Table 2: GVHD Organ Severity Criteria[¥]

Organ	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Maculopapular rash on <25% body surface area	Maculopapular rash ≥25% to ≤50%	Generalized erythroderma	Generalized erythroderma plus bullae and desquamation
GI Tract[†]	Diarrhea Adult: <500mL/day or <280 mL/m^2 Child: <10 mL/kg/day	Diarrhea Adult: 500- 1000 mL/day or 280-555 mL/m^2 Child: 10-19 mL/kg/day	Diarrhea Adult: 1001- 1500 mL/day or 556-833 mL/m^2 Child: 20-30 mL/kg/day	Diarrhea Adult: >1500 mL/day or >833 mL/m^2 Child: >30 mL/kg/day	Severe abdominal pain with or without ileus or stool with frank blood or melena (regardless of stool volume)
Upper GI Tract	No protracted nausea and vomiting	Persistent nausea, vomiting, or anorexia	–	–	–
Liver[‡]	Bilirubin <2 mg/dL	Bilirubin 2.1-3.0 mg/dL	Bilirubin 3.1-6.0 mg/dL	Bilirubin 6.1-15 mg/dL	Bilirubin >15 mg/dL

[¥]Sources:

1. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. British journal of haematology. 1997;97(4):855-864. [23]
2. Carpenter PA, Macmillan ML. Management of acute graft-versus-host disease in children. Pediatric clinics of North America. 2010;57(1):273-295. [24]
3. Childhood Hematopoietic Cell Transplantation (PDQ®): Children's Oncology Group/Pediatric Blood and Marrow Transplant Consortium consensus. National Cancer Institute at the National Institutes of Health; 2014. Available at: ***http://www.cancer.gov/cancertopics/pdq/treatment/childHCT/HealthProfessional/page4***. [25] †
   For gastrointestinal (GI) staging, adult stool output values should be used for patients weighing >50 kg. Use 3-day averages for GI staging based on stool output. If stool and urine are mixed, stool output is presumed to be 50% of total stool/urine mix.

[‡]No modification of liver staging for other causes of hyperbilirubinemia

Table 3: IBMTR and Glucksberg Grades from Organ Stage

IBMTR Grade	Glucksberg Grade	Skin	Intestine	Liver
A	I	1	0	0
B	I	2	0	0
B	II	0-2	1	0-1
B	II	0-2	0-1	1
C	II	3	1	0-1
C	II	3	0-1	1
C	II	3	0	0
B	III	0-2	2	0-2
B	III	0-2	0-2	2
C	III	0-3	0-3	2-3
C	III	3	2-3	0-3
D	III	0-3	0-3	4
D	IV	0-3	4	0-4
D	IV	4	0-4	0-4

Source: Cahn JY, Klein JP, Lee SJ, et al. Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. Blood. 2005;106(4):1495-1500. [22]

Note: Below organ stages not included in the above table can be graded as follows:

3 skin, 1 lower GI and 0 liver = Grade C
2 skin, 3 lower GI and 0 liver = Grade C
2 skin, 3 lower GI and 1 liver = Grade C
1 skin, 3 lower GI and 0 liver = Grade C
1 skin, 3 lower GI and 1 liver = Grade C
0 skin, 3 lower GI and 0 liver = Grade C
0 skin, 3 lower GI and 1 liver = Grade C

1.4 Clinical Endpoints for Evaluation of aGVHD Treatment

An important step in evaluating new treatment for aGVHD is to establish meaningful clinical endpoints that would enable effective comparison of clinical benefit between different treatment agents. Until recently, no formal guidance or recommendations existed regarding the appropriate clinical endpoints for assessing aGVHD treatment.

As with other diseases with grave prognosis, the risk of death associated with aGVHD is considerable. Thus, endpoints for aGVHD trials that indicate clinical benefit would, appropriately, be those related to improvement in survival. [26]

Response to treatment at a fixed time points after initiating treatment, including complete response (CR), overall response (OR), partial response (PR) and very good partial response (VGPR), as defined in Table 4, have been shown in several studies to be associated with improvement in mortality up to 2 years post-transplant. [1,2,26,27] In particular, OR, as defined in Table 4, to treatment at Day 28 was associated with non-relapse mortality at 6 months and 2 years [28,29] and has been supported by a number of different studies as a surrogate endpoint for transplant-related mortality. [28,30,31] VGPR, which describes a state of near CR, with a few

qualifiers, as described in Table 4, was an endpoint that was also recommended by an expert panel of the American Society for Blood and Marrow Transplant (ASBMT) in 2009 in response to the consensus that CR was too stringent an endpoint, while PR was an inadequate measure of response. [29]

Table 4: Acute GVHD Response Criteria

Abbreviation	Definition
CR	Complete response: resolution of aGVHD in all involved organs
PR	Partial response: organ improvement of at least one stage without worsening of any other organ
OR	Overall Response: Includes both CR + PR
VGPR†	Very good partial response: Fulfillment of the CR criteria with the exception of one or more of the following: Skin- No rash, non-progressive stage 1 rash, or residual erythematous rash involving <25% of the body surface without bullae (not including residual faint erythema or hyperpigmentation) Liver- Resolving elevations of total serum bilirubin concentration or total serum bilirubin concentration of <2 mg/dL or <25% of baseline at enrollment Gut- Minimal gastrointestinal symptoms, as described below: Tolerating food or enteral feeding Predominantly formed stools No overt GI bleeding or abdominal cramping No more than occasional nausea or vomiting
MR	Mixed response: improvement in at least one evaluable organ stage with worsening in another
NR	No response: no change in any organ stage in any organ system and no improvement in organ stage
Progression	Deterioration in at least one organ system by one stage or more with no improvement in any other organ
Responder	Subjects who achieve an OR§
Non-Responder	Subjects who do not achieve OR§

aGVHD=acute graft versus host disease.
† From Martin PJ, Bachier CR, Klingemann HG, et al. Endpoints for clinical trials testing treatment of acute graft-versus-host disease: a joint statement. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2009;15(7):777-784. [26]
§ In summaries of Complete Response, a responder is defined as a subject who achieves a CR and non-responder is a subject who does not achieve a CR.

1.5 Mesenchymal Stromal Cells (MSCs)

[redacted]

MSCs have been shown to attenuate inflammatory and immunological processes relevant to GVHD. MSCs demonstrate immunosuppressive activity in T cell-driven immune responses in animal models of allogenic skin graft rejection and GVHD. [32-34] *In vitro*, MSCs suppress T-cell proliferation in response to allo-antigenic and mitogenic stimulation, and stimulate an increase in the regulatory T cell (Treg) population. [35-37] Data suggest that Tregs play an important role in inhibiting allogeneic T cell response and aGVHD. [6,38] In co-culture systems, MSCs alter the cytokine secretion profile of immune cells (dendritic cells, naïve and effector T cells, natural killer cells), decreasing expression of pro-inflammatory cytokines (e.g. IFNγ, TNFα) and increasing secretion of anti-inflammatory cytokines (e.g. IL-4, IL-10) [32] The immunomodulatory effects of MSCs are attributable, at least in part, to secretion of soluble factors such as PGE2. [32] In addition, MSCs may mediate tissue protection and repair at sites of injury in GVHD by secretion of soluble factors that are known to mediate processes such as inhibition of apoptotic cell death, recruitment of endogenous stem cell populations and angiogenesis. [39-41]

[redacted]

1.7 Clinical Studies of MSCs

MSCs have been used for immunologic, gastrointestinal, and cardiac indications in humans, as described below and summarized in Table 6 and Table 7.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.7.8 Potential Risks of MSCs

A list of adverse events (AEs) possibly or probably related to remestemcel-L use is found in the Investigators Brochure. All AEs were events commonly expected in the treated population, independent of the infusions of hMSCs. The most common AEs observed for remestemcel-L in clinical trials of pediatric GVHD were infections, gastrointestinal disorders, and respiratory, thoracic and mediastinal disorders.

Infusion reaction though, uncommon (≥1/1,000 to ≤1/100), has been reported in subjects treated with remestemcel-L. An acute infusion reaction may include fever, chills, urticarial, hypotension, shortness of breath, difficulty breathing, hypoxia or other signs of acute respiratory distress.

Infusional toxicity was evaluated by continuously monitoring the subject's vital signs and oxygen saturation via pulse oximetry from the time of investigational agent infusion until two hours after starting the infusion of study drug. To reduce the potential for infusion reaction, it is recommended that subjects receive premedication with hydrocortisone and diphenhydramine. Premedication should occur 30-60 minutes prior to infusion of remestemcel-L.

Due to the known in vitro immune modulating effects of human MSCs, there is a risk of immune suppression and increased infection risk. Subjects undergoing treatment for GVHD are typically severely immunocompromised. Treatment with remestemcel-L may lead to further immunosuppression. Therefore, the potential exists for an increased risk of infectious complications. Careful subject monitoring and appropriate anti-infective prophylaxis is recommended.

With consideration of the low incidence of ectopic tissue formation from the safety data, the risk of high radiation exposure from computed tomography (CT) scans, the required administration of contrast agents, and the potential need for anesthetics in an ailing pediatric subject population, **Investigators may choose to omit CT/MRI scans at their own discretion, provided the rationale for omission is documented in the source documents.**

In theory, cells grown and expanded outside the body have the potential to be contaminated, and infection could be introduced to the subject at the time of infusion. This risk is made negligible by processing cells in a Good Manufacturing Practice (GMP)-compliant production facility, utilizing a closed system, and then by reconstituting the cells in a processing facility immediately prior to administration. The potential risks of introducing a donor-derived infectious agent are minimized by strict adherence to the 21CFR1271 Subpart C Donor Eligibility and multiple

screenings of remestemcel-L for adventitious agents prior to release. The IB contains a full list of donor screening tests performed on all lots of remestemcel-L during production.

[redacted]

[redacted]

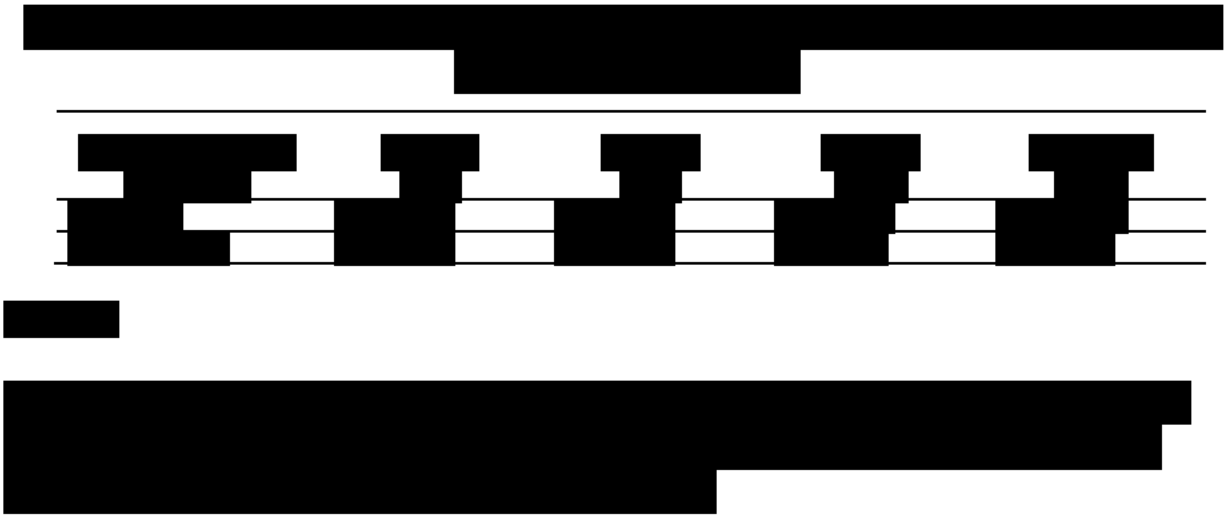
Remestemcel-L contains dimethyl sulfoxide (DMSO) [redacted] In non-clinical studies, DMSO has been reported to have potential adverse effects on the heart through negative inotropic or chronotropic actions on myocardium and decreased heart rates. In addition, DMSO has been associated with histamine release following degranulation of mast cells. Subjects that have a known allergy to sulfa drugs should be closely monitored for development of possible immune sensitivity reaction. In order to minimize potential reactions to DMSO, the subject is premedicated with diphenhydramine and hydrocortisone prior to infusion of remestemcel-L.

There has been no experience with pregnant women receiving infusions of remestemcel-L. The effects of remestemcel-L infusion on the developing fetus have not been established pre-clinically or in clinical trials. All females of childbearing potential and post-pubescent males with female partners of childbearing potential are to consent to use an effective method of birth control during this treatment protocol in a manner such that risk of failure is minimized.

1.7.9 Benefits

[redacted]

[redacted]



2. CLINICAL RATIONALE

2.1 Rationale for the Study

There are currently no FDA-approved therapies for aGVHD. Standard front-line treatment generally consists of corticosteroid, which produce a complete response in about half of all patients. [13] Even with the availability of corticosteroid, approximately 10% to 30% of aGVHD patients develop more severe aGVHD of Glucksberg Grades III or IV. [5] A variety of immunosuppressants are currently used as second-line therapy, though none of these have established efficacy against steroid-refractory aGVHD. [45] The reported one-year survival rate for patients that do not respond to steroid therapy ranges from 5% to 30%. [6,8,15-19] There is thus a strong need for agents with demonstrated efficacy for treating steroid-refractory aGVHD. Results of clinical studies to date suggest remestemcel-L provides clinical benefit in adult and pediatric patients for treating aGVHD that has failed to respond to corticosteroid. Accordingly, this study will assess the efficacy and safety of remestemcel-L in pediatric patients with aGVHD refractory to corticosteroid.

2.1.1 Rationale for Study Design

While a prospective, randomized, double-blind, placebo-controlled trial is an established benchmark clinical trial design to obtain high quality data on experimental therapy drugs, it would be neither ethical nor feasible to conduct this type of study for remestemcel-L in pediatric subjects with aGVHD. There is a small but growing body of publications reporting the benefits of remestemcel-L for aGVHD in pediatric patients. [34,42,46-52] The increasing acceptance of remestemcel-L as a beneficial treatment for aGVHD may hamper the recruitment of subjects into a randomized, placebo-controlled study, where a critically ailing young population may be

randomized to a placebo group. With this anticipated limitation, this study will be single-arm, open-label, with a planned enrollment of at least 60 subjects aged 2 months to 17 years inclusive diagnosed with Grades B-D aGVHD who fail to respond to first-line corticosteroid treatment.

The primary endpoint in this study will be OR, defined as complete response (CR) or partial response (PR), as described in Table 4, at 28 days after treatment initiation with remestemcel-L. Response to treatment at a fixed time point after initiating treatment have been shown in several studies to be associated with improvement in mortality up to 2 years post-transplant. [28-31] In particular, OR, as defined in Table 4, to treatment at Day 28 was associated with significantly lower rate of non-relapse mortality at 6 months and 2 years. [28-30] Response at Day 28 has been supported in a guideline issued by an expert panel of the American Society for Blood and Marrow Transplant (ASBMT) in 2009 as well as by subsequent studies [28,30,31]; therefore OR at Day 28 is considered an appropriate primary endpoint for efficacy evaluation of treatment for aGVHD.

2.1.2 Rationale for Subject Population

Analysis of remestemcel-L's treatment effects in the absence of other prior or concomitant second-line therapy for aGVHD presents an opportunity to discern remestemcel-L's efficacy without the potentially confounding effects of other treatment agents. [redacted]

To confirm the results of this pooled analysis, this study will evaluate the efficacy and safety of remestemcel-L in pediatric subjects with aGVHD that has failed to respond only to first-line systemic steroid treatment. The trial will exclude subjects who have received second-line treatment for aGVHD prior to study screening, in order to evaluate remestemcel-L's effects in the absence of other second-line agents.

Based on results from previous clinical studies, which demonstrated that remestemcel-L conferred clinical benefit primarily to subjects with aGVHD involving the liver and/or GI, subjects with Grade B skin-only involvement will be excluded. Accordingly, subjects in this study may have Grade C or D aGVHD involving the skin, liver, and/or gastrointestinal (GI) tract or may have Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease.

[redacted]

2.1.3 Rationale for Dosing Regimen and Treatment Period

In early studies, subjects infused with hMSCs for the treatment of steroid refractory, severe acute GVHD have experienced improvement in their GVHD, as manifested by complete resolution of GVHD symptom by 6 of 14 subjects after one to three infusions of hMSCs with a median dose of 1 x 10^6 MSCs per kilogram. [42,43] This dosing regimen of hMSC was also well-tolerated. [42,43,50] Based upon this experience, 1 – 2 x 10^6 MSCs per kilogram was deemed sufficient therapeutic benefit to aGVHD patients. [redacted] Based upon these combined data, the

planned infusional dose for this study is 2 x 10^6 hMSCs/kg actual body weight at screening, twice per week for each of 4 consecutive weeks, with at least 3 days between infusions, for the first 4weeks.

3. STUDY OBJECTIVES

3.1 Hypothesis

Mesenchymal stromal cells (MSCs), the primary component of remestemcel-L, are non-hematopoietic cells isolated from adult bone marrow and expanded in culture. *In vitro* studies show that MSCs can inhibit alloantigen- and mitogen-stimulated T cell proliferation and promote an increase in the proportion of regulatory T cells, (T_{reg}), which play an important role in inhibiting allogeneic T cell response in aGVHD. [54,55] In clinical studies, MSCs elicited improved clinical response over placebo in subjects with aGVHD. We hypothesize that remestemcel-L will display efficacy for treating aGVHD that has failed to respond to first-line steroid treatment in pediatric subjects.

3.2 Primary Objectives

1. To evaluate the efficacy of remestemcel-L in pediatric subjects with Grades B-D aGVHD who have failed to respond to steroid treatment post allogeneic HSCT.
2. To gather additional information on the safety of remestemcel-L in pediatric subjects with Grades B-D aGVHD that has failed to respond to steroid treatment post allogeneic HSCT.

3.3 Secondary Objectives

1. To determine the correlation between response to remestemcel-L at Day 28 and survival at Day 100.
2. To obtain quality of life data on remestemcel-L-treated subjects via the Pediatric Quality of Life Inventory™ (PedsQL™; Appendix 1 and Appendix 2) and the pediatric global health-related quality of life (HRQOL) Parent Proxy Report (Appendix 3).
3. To measure the functional status of remestemcel-L-treated subjects using the Karnofsky/Lansky scale (Appendix 4).

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design and Dosing Regimen

This trial is a prospective, single-arm study involving multiple study centers, to evaluate the efficacy and safety of remestemcel-L in pediatric subjects with acute GVHD who have failed to respond to systemic steroid treatment. The study plans to treat at least 48 pediatric subjects, male and female, between the ages of 2 months and 17 years inclusive with aGVHD following allogeneic hematopoietic stem cell transplant (HSCT) that has failed to respond to treatment with systemic corticosteroid therapy. Subjects may have Grades C and D aGVHD involving the skin, liver and/or gastrointestinal (GI) tract or Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease.

Subjects will be treated with intravenous (IV) remestemcel-L at a dose of 2 x 10^6 MSC/kg actual body weight at screening, twice per week for each of 4 consecutive weeks. Eligible subjects will receive Continued Therapy, an additional 4 once weekly infusions of remestemcel-L at the same initial dose of 2 x 10^6 MSC/kg actual body weight at screening. Eligible subjects may also receive GVHD flare therapy, which consists of an additional 4 twice-weekly infusions of remestemcel-L at the same initial dose of 2 x 10^6 MSC/kg actual body weight at screening.

4.1.1 Primary Endpoint

The primary endpoint will be overall response (OR), defined as complete response (CR) or partial response (PR; see Table 4), of the study population at 28 days post initiation of therapy (Day 0) with remestemcel-L.

4.1.2 Secondary Endpoints

The secondary endpoints in this study will be the following:

1. Overall survival at Day 100 post initiation of remestemcel-L therapy
2. Rate of very good partial response (VGPR) at Day 28 post initiation of remestemcel-L therapy
3. Rates of OR and VGPR at Day 100 post initiation of remestemcel-L therapy
4. Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy, stratified by organ involvement
5. Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy, stratified by individual subject organ involvement
6. Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy, stratified by baseline aGVHD grade

7. Overall survival at Day 100 post initiation of remestemcel-L therapy, stratified by baseline aGVHD grade and organ involvement
8. Rate of aGVHD progression requiring additional GVHD medications/ therapy through Day 100 post initiation of remestemcel-L therapy
9. Effect of additional remestemcel-L therapy after Day 28 on rate of OR and VGPR at Days 56 and 100 post initiation of remestemcel-L therapy.

4.1.4 Treatment Plan

A summary of the treatment plan is presented in Table 10.

Table 10: Summary of Treatment Plan

	Initial Therapy	Continued Therapy	Flare Therapy
Dose†	2 x 10^6 MSC/kg	2 x 10^6 MSC/kg	2 x 10^6 MSC/kg
Frequency	Twice per week	Once per week	Twice per week
Duration	4 consecutive weeks	4 consecutive weeks	4 consecutive weeks
Timing of Treatment Initiation	Within 4 days of signing of informed consent. All infusions must be completed by Day 28 ± 2 days.	Within 1 week after 28-day assessment. All infusions must be completed within 28 days ± 2 days.	After 28-day assessment and before Day 70
Subjects Eligible for Dosing	Subjects who meet all Inclusion/ Exclusion criteria	Subjects with Partial Response (PR) or Mixed Response (MR) based on the Day 28 therapy assessment	Subjects who have a GVHD flare of Grade B-D after achieving a Complete Response (CR) and before Day 70
Subjects <u>not</u> Eligible for Dosing	Subjects who do not meet all Inclusion/ Exclusion criteria	Subjects with Complete Response (CR) or No Response (NR) based on the Day 28 therapy assessment Subjects who have begun other second-line GVHD therapy	Subjects who do not achieve a Complete Response (CR) Subjects who have a GVHD flare of Grade B-D after Day 70. Subjects who have begun other second-line GVHD therapy.
†Based on actual screening body weight			

4.1.4.1 Initial Therapy

Subjects will be administered remestemcel-L intravenously (IV) at a dose of 2 x 10^6 MSC/kg actual body weight at screening, twice per week, for each of the first 4 consecutive weeks of treatment with infusions administered at least 3 days apart and no more than 5 days apart for any infusion. All 8 infusions must be administered by Day 28 ± 2 days (Table 10).

Subjects may continue to be treated with a stable dose of systemic steroid therapy until they are eligible for steroid taper and may continue on an established regimen of baseline prophylactic therapy following initiation of remestemcel-L (Day 0). No other medications for the treatment of aGVHD are to be introduced to subjects during the initial 28 days post remestemcel-L administration unless disease progression, as defined below, has occurred. Addition of other secondary line agents prior to Day 28 would constitute failure to respond, in which case, the treated subject would remain on the study for safety follow up.

Any changes in baseline prophylaxis regimen should be recorded in the eCRF and reason for change in regimen should be discussed with the Medical Monitor. Changes in dose or prophylactic agent due to administration route intolerance or toxicities are allowed at the discretion of the investigator with prior approval from the Medical Monitor as these changes could be confused as second-line therapies.

4.1.4.2 Continued Therapy

Eligible subjects will receive an additional 4 once weekly infusions of remestemcel-L at the same initial dose of 2 x 10^6 MSC/kg actual body weight at screening, which will begin within one week after the Day 28 assessment (Table 10). Infusions will be given once weekly (± 2 days) and all 4 infusions must be administered within 28 days (±2 days). No additional treatment with remestemcel-L is allowed at any other point in time unless the criteria for GVHD flare, as defined in this protocol, is met.

4.1.4.3 Eligibility for Continued Therapy

Eligibility to receive additional therapy after the initial 4-week treatment period is dependent upon the results of the subjects' response assessments, as defined in Table 4, at Day 28, as follows (Table 10):

Complete response (CR): If a subject displays CR, then no additional remestemcel-L will be administered.

No Response (NR): If a subject displays NR, then no additional remestemcel-L infusion will be administered.

Partial Response (PR): If a subject displays PR, the subject will receive Continued Therapy.

Mixed Response (MR): If a subject displays MR, the subjects will receive Continued Therapy.

4.1.4.4 GVHD Flare

Subjects who have a GVHD flare of Grade B-D after achieving a CR (after Initial or Continued Therapy) and before Day 70 may receive additional remestemcel-L treatment per the Initial Therapy plan (Table 10). GVHD flare is defined as any increase in aGVHD symptoms (measured by GVHD grade B-D) beyond 28 days post first infusion, subsequent to achieving CR to Initial Therapy, or beyond Day 56 after achieving CR to Continued Therapy. If a subject has begun other second-line GVHD therapy, he or she would be ineligible to receive any further

remestemcel-L therapy upon receiving the other second-line GVHD therapy. Subjects are eligible for a single treatment for flare.

4.1.4.5 Other GVHD therapy

If a subject begins other second-line GVHD therapy within the period of Initial and Continued Therapy (through Day 56, if applicable), he or she would be considered to have failed treatment and would be ineligible to receive any further remestemcel-L therapy upon receiving the other second-line GVHD therapy.

Changes in prophylaxis regimen (change in dose or prophylactic agent) due to administration route intolerance or toxicities are allowed at the discretion of the investigator with prior approval from the Medical Monitor and are not considered second-line therapies.

4.2 Study Duration

Enrolled subjects will receive Initial Therapy for 4 weeks; eligible subjects will receive therapy for an additional 4 (Continued Therapy) to 8 (Flare Therapy) weeks. Subjects will be assessed according to a schedule of planned assessments, as summarized in Table 11, and will be followed for up to 100 days. The total duration of study participation per subject will be up to 111 days to account for the 4-day screening window and end of study visit ±7 days.

4.3 Extension Follow-up Study of Safety and Health Outcomes

An extension study under a separate protocol (MSB-GVHD002), subsequent to the present study, is being conducted in order to capture health outcomes and safety data out to Day 180.

Table 11: Schedule of Assessments and Procedures

	Screening/Baseline	Treatment	Study Visits										
Study Days	**Day -4 to Day -1**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28[f]**	**Day 35**	**Day 42**	**Day 49**	**Day 56**	**Weekly (From Day 63 to Day 100)[a]**	**End of Study Day 100**	
Visit window	**N/A**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**Unscheduled**
Infusions [a, b, c, d]	**No infusions scheduled**	**← ← Infusions 2x per week → →**						**If eligible, infusions 1x per week (continued therapy) or 2 x per week (flare therapy)**				**No infusions scheduled**	
Screening/Baseline/Follow-up Assessments													
Demography/informed consent [e]	X												
Inclusion/exclusion criteria	X												
Vital signs (HR, BP, Temp, RR, Oxygen Saturation)	X	X		X	X	X	X	X	X	X	X	X	X
Height and weight	X											X	X
Physical examination	X	X		X	X	X	X	X	X	X	X	X	X
CMV screening [f]	X		X	X	X	X	X	X	X	X	X	X	X
HIV and hepatitis testing [g]	X												
Oncology history: Underlying malignant or leukemic disease/conditioning regimen/HSCT/diagnosis of initial GVHD/diagnosis of steroid refractory GVHD	X												
Medical history and current conditions	X												
Hospitalization information (if applicable) [h]	X					X						X	X
Hematology laboratory tests [i]	X					X						X	X
Chemistry laboratory tests	X					X						X	X
Urinalysis	X					X						X	X
ESR (local labs only)	X					X						X	X

	Screening/Baseline	Treatment	Study Visits										
Study Days	**Day -4 to Day -1**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28[f]**	**Day 35**	**Day 42**	**Day 49**	**Day 56**	**Weekly (From Day 63 to Day 100)[a]**	**End of Study Day 100**	
Visit window	**N/A**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**Unscheduled**
Infusions [a, b, c, d]	**No infusions scheduled**	**← ← Infusions 2x per week → →**						**If eligible, infusions 1x per week (continued therapy) or 2 x per week (flare therapy)**				**No infusions scheduled**	
Screening/Baseline/Follow-up Assessments													
Acute GVHD assessment (Skin, Lower GI, Upper GI, Liver) [a, b]	X			X	X	X	X	X	X	X	X	X	X
Chronic GVHD Assessment	X			X	X	X	X	X	X	X	X	X	X
Prior and concomitant medication [k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusion [l]													X
[Optional] CT scan or MRI (Chest, Abdomen and Pelvis) [m]	X											X	X
12-Lead ECG	X											X	X
Karnofsky or Lansky scale [n]	X					X				X		X	X
Quality of Life Measures [o]	X					X				X		X	X
Termination/end of study												X	X
TREATMENT													
Investigational agent infusions [c, d, p]		X	X	X	X	X	X	X	X	X			X
Investigational agent pre-medication		X	X	X	X	X	X	X	X	X			X
Continued/flare treatment [d,k]						X				X			X
Therapy assessment/current GVHD response status [b]				X	X	X	X	X	X	X	X	X	X
SAFETY ASSESSMENTS													
Pregnancy test [q]	X									X		X	X
Adverse event evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusional toxicity [r]		X	X	X	X	X	X	X	X	X	X		X

a. Weekly GVHD assessments must be performed after infusion of the 2nd dose of remestemcel-L for that week. The weekly assessment visits should be conducted at least 24 hours after the most recent remestemcel-L infusion.

b. The Day 28 and Day 56 assessments **must** be at least 24 hours after the last dose of remestemcel-L is administered.

	Screening/Baseline	Treatment	Study Visits										
Study Days	**Day -4 to Day -1**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28[f]**	**Day 35**	**Day 42**	**Day 49**	**Day 56**	**Weekly (From Day 63 to Day 100)[a]**	**End of Study Day 100**	
Visit window	**N/A**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**Unscheduled**
Infusions [a, b, c, d]	**No infusions scheduled**	**← ← Infusions 2x per week → →**						**If eligible, infusions 1x per week (continued therapy) or 2 x per week (flare therapy)**				**No infusions scheduled**	
Screening/Baseline/Follow-up Assessments													

c. Infusion will be administered at least 3 days apart and a maximum of 5 days apart. All 8 infusions (Initial therapy) must be administered within 28 days (± 2 days). All infusion doses will be based on weight determined at screening.

d. Eligible subjects will receive an additional 4 once weekly infusions (± 2 days) within 1 week after Day 28 until Day 56. Subjects who have a GVHD flare of Grade B-D after achieving a CR at day 28 or day 56 (following Continued Therapy) and before day 70 may receive additional remestemcel-L treatment per the Initial Therapy plan.

e. When possible, subjects should be presented with the IRB/EC approved consents for MSB-GVHD001 and MSB-GVHD002 simultaneously at the time of consent onto this protocol.

f. CMV screening will be conducted weekly during the study. Investigators should provide standard of care treatment for viral infections as appropriate, including prophylaxis and treatment if there is evidence of viral reactivation and/or infection.

g. If HIV and/or hepatitis testing was performed within 3 months of screening, the results from these tests may be used instead. The determination of active hepatitis B or C is at the discretion of the Investigator.

h. Record all hospital stays occurring during the course of the trial starting with the hematopoietic stem cell (HSC) transplant hospitalization.

i. Collection for local labs should be performed for all patients at screening. If the age/weight of the subject permits, collection for central labs should also be performed at screening, in addition, in order to facilitate comparison of later samples sent to the central lab. If age/weight of the patient does not allow for this additional blood volume, then local labs at screening will serve as baseline labs. Viral screening will also be performed at screening with exception of CMV, which will be conducted as noted in the table above.

[redacted]

k. Remestemcel-L treatment for flare to be added where applicable. Flare therapy must be initiated before Day 70.

l. Total number of units transfused of blood product will be recorded in the eCRF during study.

m. CT/MRI scans are optional and may be omitted at the discretion of the Investigator, provided the rationale for omission is documented in the source documents.

n. Lansky scale for subjects less than 16 years of age; Karnofsky for subjects 16 years of age and older. See Appendix 4 for the Karnofsky and Lansky scales.

o. Quality of life will assessed using the Pediatric Quality of Life Inventory™ (PedsQL™) and the pediatric global health-related quality of life (HRQOL) Parent Proxy Report

p. Infusions noted in this table are limited to those just prior to assessments

q. A serum pregnancy test will be performed at Screening for all females with child bearing potential (≥10 years of age). Post-screening, a urine dipstick pregnancy test will be performed on all females with childbearing potential (subjects ≥10 years of age) at Day 56, Day 100, and for Unscheduled Visits. If there is a positive urine dipstick, a serum sample should be sent to central lab for confirmation. Guidance on childbearing potential and pregnancy testing is located in Appendix 6.

r. Infusional toxicity on each day of remestemcel-L administration from the start of infusion to two hours after start of IMP administration. See Table 13.

4.4 Number of Subjects Assigned to Treatment Groups

This is a single-arm study in which at least 48 enrolled subjects will be treated with remestemcel-L.

4.5 Study Sites

This study will be conducted in approximately 35 different sites.

5. STUDY POPULATION

5.1 Overview

The study plans to treat at least 48 pediatric subjects, male and female, between the ages of 2 months and 17 years inclusive. Subjects may have Grades C and D aGVHD involving the skin, liver and/or gastrointestinal (GI) tract or Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease.

5.2 Eligibility Criteria

5.2.1 Informed Consent

The informed consent document will be used to explain the risks and benefits of participation to the patient and/or the patient's guardian in simple terms prior to treatment. Written authorization for use and disclosure of personal health information (PHI) as per the requirements under the Health Insurance Portability and Accountability Act (HIPAA) (45 CFR 164) or per local privacy regulation must be obtained as part of the informed consent process. Authorization can be included in the informed consent form or can be issued as a separate document. The treating physician is responsible for ensuring that written informed consent, including written authorization for use and disclosure of PHI and appropriate signatures and dates, is obtained from each patient before any protocol-related procedures including any pre-treatment procedures are performed. As subjects treated with remestemcel-L under this protocol will be under 18 at the time of informed consent, a signature from a parent or legal guardian indicating informed consent will be required.

The informed consent document must include the elements required by Food & Drug Administration (FDA) regulations in the Code of Federal Regulations (21 CFR Part 50), written authorization for use and disclosure of PHI (45 CFR 164) and International Conference on Harmonization (ICH) guidelines, as applicable. The treating physician agrees to obtain approval from Mesoblast International Sàrl (Mesoblast) of any informed consent and written authorization

for use and disclosure of PHI authorization document used in the execution of the protocol, prior to submission to the Institutional Review Board (IRB) or Ethics Committee (EC). In the event the subject is re-screened for participation, a new and written authorization for use and disclosure of PHI document must be signed.

An extension study under a separate protocol (MSB-GVHD002), subsequent to the present study, is being conducted in order to capture health outcomes and safety data out to Day 180. Subjects may be presented with the IRB/EC approved consents for MSB-GVHD001 and MSB-GVHD002 simultaneously at the time of consent onto this protocol.

5.2.2 Inclusion Criteria

Subjects are eligible for the study if all of the following criteria are met:

1. Subject was diagnosed with Grade B-D acute GVHD requiring corticosteroid systemic therapy. The subject may have Grade C or D aGVHD involving the skin, liver, and/or gastrointestinal (GI) tract or may have Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease. Acute GVHD is defined as the presence of skin rash and/or persistent nausea, vomiting, and/or diarrhea and/or cholestasis presenting in a context in which aGVHD is likely to occur and where other etiologies such as drug rash, enteric infection, or hepatotoxic syndromes are unlikely or have been ruled out.
2. Subject is 2 months to 17 years of age, inclusive.
3. Subject has failed to respond to steroid treatment, with failure to respond defined as any Grade B-D (IBMTR grading) aGVHD that shows progression within3 days or no improvement within 7 days of consecutive treatment with 2 mg/kg/day of methylprednisolone or equivalent.
4. Subject must be able to be treated with remestemcel-L within 4 days of signing of informed consent.
5. Subjects who have had persistent GI GVHD manifested by diarrhea with stool volume less than 500 mL/day (for subjects >50 kg) or less than 30 mL/kg/day(for subjects ≤50 kg). See Table 2: GVHD Organ Severity Criteria for values in ml/m^2. In the absence of nausea or vomiting, subject may still be considered to have Grade B GVHD if:
    a. other causes of diarrhea have been ruled out (e.g., C. difficile, adenovirus or cytomegalovirus (CMV) infection, oral magnesium administration) and if
    b. the low stool volume reflects the effects of fasting, narcotics, or anti-diarrheal medications.

6. Subject must have adequate renal function as defined by a calculated creatinine clearance of >30 mL/min per 1.73 m^2. For subjects 1 to 18 years of age creatinine clearance should be calculated using the Bedside Schwartz equation:[56,57]

   GFR (ml/min per 1.73 m^2) = [0.413 × height (cm)]/Serum creatinine (mg/dl)

   For subjects less than 1 year old, renal function should be determined using the Schwartz equation adjusted for this age group:

   Creatinine clearance (ml/min per1.73 m^2)= (height [cm] x 0.45)/ (serum creatinine [mg/dL])

7. Subject has a minimum Karnofsky/Lansky Performance Level of 30 at the time of study entry.
8. Subject (or legal representative where appropriate) must be capable of providing written informed consent.
9. Female subjects of childbearing potential (≥ 10 years of age) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for the follow-up time period. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method. Guidance on childbearing potential and pregnancy tests are located in Appendix 6.
10. Male subjects with partners of childbearing potential must agree to use adequate contraception (barrier method or abstinence) during the study, including the follow-up time period.
11. The subject must be willing and able to comply with study requirements, remain at the clinic, and be willing and able to return to the clinic for the follow-up evaluation, as specified in this protocol during the study period.

5.2.3 Exclusion Criteria

Subjects will not be eligible for participation in the study if they meet ANY of the following criteria:

1. Subject has Grade B aGVHD with skin-only involvement.
2. Subject has received any second line therapy to treat aGVHD prior to screening.

3. Subject has received systemic agents other than steroids and prophylactic agents for primary treatment of acute GVHD.
4. Subject shows evidence of diffuse alveolar hemorrhage or other active pulmonary disease, which is likely to require more than 2L of oxygen via face mask or an estimated FiO_2 of 28% via other delivery methods in order to sustain an O_2 saturation of 92%.
5. Subject has any underlying or current medical or psychiatric condition that, in the opinion of the Investigator, would interfere with the evaluation of the subject including but not limited to uncontrolled infection, heart failure, pulmonary hypertension, etc.
6. Subject has received any stem cell agents (other than hematopoietic graft) during study participation or within 30 days prior to study entry. Donor Leukocyte Infusion (DLI) is excluded during study participation or within 30 days prior to study entry. Previous use of irradiated granulocytes within 30 days is permitted.
7. Subject has received an HSCT transplant for a solid tumor disease.
8. Subject has had prior treatment with mesenchymal stromal cells (MSCs), including remestemcel-L.
9. Subject shows evidence of severe (require treatment) hepatic veno-occlusive disease (VOD) or sinusoidal obstruction at screening.
10. Subject has had positive laboratory test results indicating infection with the human immunodeficiency virus (HIV) at any time and/or active hepatitis B or C virus infection within 3 months prior to screening.
11. Subject shows evidence of encephalopathy as defined by a change in mental status since the onset of aGVHD.
12. Subject is a female who is pregnant, lactating, or is planning a pregnancy during study participation, or in the follow-up period.
13. Subject is currently being treated for a solid tumor malignancy.
14. Subject has participated in any interventional clinical trial for an aGVHD therapeutic agent. However, in exceptional cases (see Section 7.9.1), experimental agents may be administered to enrolled subjects at the Investigator's discretion.
15. Subject has participated or is currently participating in any autologous or allogeneic stem cell or gene therapy study for the treatment of aGVHD. Patients participating in investigative protocols aimed at modification of the transplant graft (such as T cell depletion) or aimed at modification of the conditioning regimen will be allowed in the study.
16. Subject has a known hypersensitivity to dimethyl sulfoxide (DMSO) or to murine, porcine, or bovine proteins.

5.3 Subject Discontinuation Criteria or Premature Subject Withdrawal

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects may be also considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up.

The Investigator may discontinue any subject for any reason that may interfere significantly with the trial procedures and/or the interpretation of results. In addition, a subject may be withdrawn from the study if the Investigator determines that continued participation in this trial would pose a significant safety risk for the subject.

At a minimum, the following should be collected when a subject discontinues:

- The reason the subject discontinued
- The date of last treatment
- The date of the last assessment and/or contact
- Adverse events (AEs), including concomitant medications used to treat AEs
- Final (end of study) Assessments.

5.3.1 Lost to Follow-Up

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the Investigator post-enrollment, after reasonable efforts have been made to contact the subject. The Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls or registered letters. The end of participation for a subject lost to follow-up is the date of the last known contact (e.g., visit or telephone contact).

5.4 Rescreening of Screen-Failed Subjects

Screen-failed subjects may be re-screened once at the Investigator's discretion. If the rescreening takes place within one week of the screen failure, only the tests the subject has failed at screening should be repeated at the rescreening. If the rescreening occurs one week or more after the initial screening, all screening tests should be repeated.

5.5 Rules for Discontinuing Investigational Medicinal Product (IMP)

Subjects may discontinue IMP under the following circumstances:

- Subject voluntarily withdraws from the study
- Subject is withdrawn from the study at the Investigator's discretion
- Subject completes study requirements
- Death.

Every effort should be made to complete the 'End of Study' assessments for all subject withdrawals / terminations.

If the subject discontinues from the treatment protocol and has an ongoing adverse experience at the time of discontinuation, the subject must receive follow-up for at least 2 weeks to clarify the nature of the AE. If clinical visit(s) are necessary, the procedures performed during the follow-up visit(s) will be recorded on unscheduled visit pages of the CRF. If the AE has not resolved after a 2-week period, a plan for further follow-up of the subject will be created by the treating physician in consultation with the Medical Monitor.

5.6 Information to be Collected for Screen Failures

Subjects who are consented and are screened for eligibility into the trial, but do not meet the inclusion/exclusion criteria for trial entry, will be considered screen failures. Subjects who provide consent but discontinue the trial prior to being given IMP will also be considered screen failures.

The following information must be recorded on the respective case report forms (CRFs) for all screen failures:

- Demography
- Inclusion/exclusion criteria
- Adverse events
- End of screening disposition.

5.7 End of Study

The end of study is defined as any one of the following, whichever occurs first:

- The date of the last scheduled visit for the last subject
- The date of death of the last subject
- The date of withdrawal of the last subject.

Individual subjects will be considered to have completed the study when they have completed all required protocol procedures and assessments. For subjects with ongoing AEs at the last scheduled visit, the end of study date will be deemed the last scheduled visit date. The study site staff will perform the appropriate closeout/last visit assessments.

5.8 Planned Follow-up Study of Safety and Health Outcomes

An extension study under a separate protocol (MSB-GVHD002), subsequent to the present study, is being conducted in order to capture health outcomes and safety data out to Day 180. Subjects may be presented with the IRB/EC approved consents for MSB-GVHD001 and MSB-GVHD002 simultaneously at the time of consent onto this protocol.

6. INVESTIGATIONAL MEDICINAL PRODUCT

[redacted]

[redacted]

6.3 Handling and Accountability

Remestemcel-L will be provided to the study sites by the Sponsor or designee. Only the Investigator(s) or their designee(s) will be permitted to administer the IMP to subjects participating in this protocol.

The IMP must be received by a person designated by the Investigator at the study site, handled and stored safely and properly, and kept in a secured location that is accessible only by the designated person(s). Upon receipt, the designee must update the IMP accountability records, including records of IMP order, and maintain and store the records in a secure location. The CRA will review the records at the monitoring visits.

Details regarding the accountability records are provided in the study Investigational Medicinal Product (IMP) Manual.

6.4 Storage of Investigational Medicinal Product

The IMP will be shipped directly either from Mesoblast or a designated central distributor to the cell processing technologist in the Cell Processing Laboratory at the study site. The IMP will be shipped to the site in the vapor phase of a liquid nitrogen cryoshipper. The IMP will be stored in the vapor phase of a secured liquid nitrogen freezer where access to the area is strictly limited to the Cell Processing Laboratory personnel. The IMP will be appropriately identified and segregated from other products. Details regarding the storage, handling, and preparation of the IMP are provided in the study IMP manual.

6.5 Destruction of the Investigational Medicinal Product

Partially used IMP will be discarded according to the study site's destruction policy, and the discarding will be recorded in the accountability log.

Local or institutional regulations may require immediate destruction of any unused IMP for safety reasons. In these cases, it may be acceptable for the investigational site staff to destroy unused IMP before a monitoring inspection, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of the quantity

of IMP that was shipped, dispensed, returned and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction of the IMP.

The unused IMP provided by the Sponsor may be returned to the Sponsor. Where local or institutional regulations permit, destruction of IMP will occur at a location designated by the Sponsor. Written authorization must be obtained from the Sponsor prior to the return or destruction of the IMP.

7. STUDY PROCEDURE

Table 11 Schedule of Assessments and Procedures, lists all planned assessments, which are marked with an "X" when the visits are performed. Subjects should be seen for all visits on the designated day or at a time that is as close as possible to the designated day. The study assessment schedule in Table 11 outlines all procedures to be performed on subjects at the scheduled visits.

In order to minimize variability in evaluations, ideally, the same individuals should perform the same tests on all the subjects at a given trial site.

7.1 Visit Schedule and Assessments

7.1.1 Screening Period

Subjects will enter the screening period once the written informed consent has been signed. The following assessments and procedures will be performed at the screening visit:

- Written informed consent and written authorization for use and disclosure of personal health information
- Physical examination
- Height and weight
- Vital Signs (heart rate [HR], blood pressure [BP], temperature, and respiratory rate [RR])
- O_2 saturation by pulse oximetry (SaO_2/SAT) monitored by pulse oximetry.
- Medical history, including any history of malignancies, and current condition
- Prior and concomitant medications

- Acute GVHD assessment (skin, lower GI, upper GI, liver)
- Chronic GVHD assessment
- CT or MRI scan of the chest, abdomen, and pelvis. Scans will contribute information with regard to baseline disease burden and will also provide baseline for evaluation of future possible ectopic tissue formation. For CT, use intravenous (IV) contrast; if IV is contraindicated for any reason, oral contrast is acceptable even in the presence of GI GVHD. A previous CT scan or MRI may be used if performed up to 90 days prior to first IMP infusion or 24 hours after IMP infusion.
  NOTE: CT/MRI scans are optional and Investigators may choose to omit CT/MRI scans at their own discretion, provided the rationale for omission is documented in the source documents.
- 12-lead electrocardiogram
- Urinalysis
- Laboratory assessments
  - Hematology (including viral screening, please see Table 12 for details)
  - Serum chemistry (including hsCRP, please see Table 12 for details)
  - ESR (local lab)
  - [redacted]
- Karnofsky/Lansky performance assessment (see Appendix 4)
- Serum pregnancy test for female subjects of childbearing potential (≥10 years of age) (see Appendix 6 for guidance on childbearing potential and pregnancy testing)
- Pediatric Quality of Life Inventory™ (PedsQL™; Appendix 1 and Appendix 2) and the pediatric global health-related quality of life (HRQOL) Parent Proxy Report (Appendix 3)
- Adverse event (AE) assessment.

7.1.2 At Each Infusion Day

IMP infusions will be given to subjects who have signed the informed consent form, completed screening, and been deemed eligible for inclusion in the study. Initial Treatment infusion of IMP must be given within 4 days after signing of informed consent. Infusions of IMP must be given at least 3 days apart and no more than 5 days apart for any infusion. All 8 infusions must be administered by Day 28 (± 2 days). Continued Therapy infusions, when applicable, will be given once weekly (± 2 days). Flare therapy infusions, when applicable, will follow the same infusion schedule as the Initial Therapy. Missed infusions will be documented on the eCRF.

On the day of infusion, the following procedures/assessments will be performed:

- Vital Signs (heart rate [HR], blood pressure [BP], temperature, and respiratory rate [RR]; please see Table 13 for time points)
- Oxygen Saturation Monitoring: [redacted]
- Physical Examination
- Pre-medication, consisting of hydrocortisone and diphenhydramine will be administered at least 30 minutes prior to the investigational agent [redacted]
- AE assessment
- Concomitant medication assessment
- Infusional toxicity assessment
- IMP administration [redacted]

- Detailed instructions on IMP preparation, handling, and administration may be found in the IMP Manual.

7.1.2.1 Special Guidance for Investigators During IMP Infusion

During IMP administration, infusion *should be stopped if:*

1. The subject shows signs of respiratory compromise such as tachypnea, cyanosis, complains of shortness of breath, etc. regardless of the oximetry reading.
2. SaO2/SAT decreases [redacted]
3. IMP infusion *may be stopped* at the discretion of the Investigator if there is an AE that the Investigator believes is related to the IMP, if there is an issue with IMP infusion, or the subject withdraws consent.

If the toxicity evaluation during an infusion resulted in a worsening of a subject's respiratory functioning by one or more grades (per the Common Toxicity Criteria for Adverse Events [CTCAE] assessment criteria, Table 14, Section 8.1.3) in comparison to the pre-infusion status, and the respiratory status did not return to baseline levels after symptomatic treatment, the Investigator must contact the Medical Monitor in order to discuss each specific case and determine whether the subject will be precluded from additional IMP infusions.

No other medications should be given during the investigational agent infusion unless determined medically necessary by the Investigator.

7.2 Efficacy Assessments

7.2.1 GVHD Assessments

GVHD assessments will be performed weekly, from Day 14 (±2 days) until Day 100 (±7 days). During assessment weeks in the Initial Therapy period, the assessments must be performed after infusion of the 2nd dose of remestemcel-L for that week (or after the 1st dose of remestemcel-L during Continued Therapy). The weekly assessment visits should be conducted at least 24 hours after the most recent remestemcel-L infusion. These weekly GVHD assessments will be used to assess the GVHD status according to the definitions which are provided for grading and determination of progression or improvement.

Rescue therapy may be administered if necessary. If new GVHD medication(s) are administered as rescue therapy based on the assessment(s), no further remestemcel-L infusions will be allowed. Subjects will otherwise remain in the study regardless of response and will continue to be evaluated per the assessment schedule.

Progression of disease is defined as deterioration of GVHD by at least one organ system by one organ stage or more from screening/baseline assessment up to Day 28 and from the most recent prior assessment from Day 28 to Day 100. Progression is not defined as 'mixed response' according to the definitions described above in Table 4.

7.2.2 Therapy Assessments

Therapy assessments will be performed at each study visit after Day 0. Assessments must be after the 2nd dose of remestemcel-L is administered for each assessment week of the Initial Therapy period (or after the 1st dose of remestemcel-L during Continued Therapy). A schedule of the planned assessments is detailed in Table 11.

Day 28 Therapy Assessment:
A therapy assessment will be performed on Day 28 (±2 days) to determine treatment response and whether a subject will be provided Continued Therapy. The Day 28 therapy assessment must be at least 24 hours after the last dose of remestemcel-L is administered. Continued Therapy will be allowed for subjects according to their response to treatment, as described in Section 4.1.4.3.

Day 56 Assessment of Response to Continued Therapy
A therapy assessment will be performed on Day 56 (±2 days) for all subjects. The Day 56 therapy assessment must be at least 24 hours after the last dose of remestemcel-L is administered for subjects receiving Continued Therapy, in order to determine treatment response to the Continued Therapy.

Ongoing GVHD assessments will be performed to assess the subjects' eligibility for flare treatment in accordance with Section 4.1.4.4.

7.3 Safety Assessments

All AEs, including those considered to have a causal relationship to the IMP, will be collected weekly at each assessment time point. AEs collected will consist of both solicited and events voluntarily reported by the subjects.

Infusional toxicity will be evaluated at each remestemcel-L administration from the start of infusion to two hours after the start of IMP administration

Measurement of all clinical parameters should be performed as described in Table 12. Standard instructions for determining these parameters are provided in the following sections.

7.3.1 Physical Examination

A physical examination, including but not limited to a targeted examination for evidence of AEs, will be performed at Screening, Day 0, and at each weekly visits from Day 14 (±2 days) until Day 100 (±7 days).

Information about physical examinations must be available in the source documentation at the study site. Significant findings that are present prior to the start of the study drug must be included in the relevant CRF on medical history/current medical conditions. Significant new findings made after the start of the study drug that meet the definition of an AE or SAE must be recorded on the Adverse Event CRF.

7.3.2 Vital Signs

Measurements of vital signs (BP, HR, respiratory rate, temperature, and oxygen saturation) should be assessed at Screening, Day 0, and at each weekly assessment from Day 14 (±2 days) through Day 100 (±7 days). Manual or automated procedures for obtaining BP are acceptable as long as the same method and same arm are used throughout the study. Measurements of vital signs will include sitting systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), oxygen saturation (SpO2, pulse oximetry), temperature, and respiratory rate (RR).

Vital signs will be measured after approximately 5 minutes of quiet rest with the subject in a sitting position. Ideally, the site should have a dedicated blood pressure machine and use the same machine and blood pressure measurement method for all subjects during the trial.

Any clinically significant findings in vital sign measurements compared with baseline measurements should be recorded as an AE.

7.3.3 Height and Weight

At the screening and end of study visits, height and weight should be measured. The weight measurement at Screening will be used to determine the dose of IMP to be used throughout the subject's treatment period.

Measurement of height from a standing position should be performed with the subject's shoes removed, the knees straightened, and head held upright. For infants, height should be measured with the child lying down, and measurements should be recorded as recumbent length.

Measurement of weight should be performed without shoes or extra layers of clothing (e.g., sweater or jacket) during the measurement. Subjects should be weighed on the same scales at all visits.

7.3.4 Electrocardiogram (ECG)

Electrocardiogram (ECG) will be performed at screening and at the End of Study/Day 100 (±7 days) to assess any changes in cardiac physiology. Subjects should be in a supine or semi-supine position for at least 5 minutes prior to the recording. The same recording position (supine or semi-supine) and the same equipment should be used for each subject throughout the study.

All ECG tracings must be (1) reviewed by a medically qualified member of the study team, (2) annotated to indicate any clinical finding, and (3) signed and dated by the medically qualified member, and (4) filed with the notes for the subjects. ECG parameters will be entered into the CRF, and if any ECG abnormality is associated with an AE, it must be entered in the AE CRF.

Heart rate, PR, QRS and QT durations should also be noted on the CRF along with the ECG parameters.

7.3.5 Adverse Events

All AEs, including those considered to have a causal relationship to the IMP, will be collected weekly at each assessment time point. AEs collected will consist of both solicited and events voluntarily reported by the subjects.

7.3.6 Assessment of Infusional Toxicity

A theoretical risk of decreased respiratory function during the infusion exists, though to date, no infusional toxicities have been reported. Infusional toxicity will be evaluated by continuously monitoring the subject's vital signs and SaO2/SAT via pulse oximetry from investigational agent administration through two hours after starting infusion.

7.3.7 Pregnancy Tests

A serum pregnancy test will be performed by the site personnel for all female subjects of childbearing potential (≥10 years of age) at screening. At post-screening visits, a urine dipstick test will be performed for all female subjects of childbearing potential (≥10 years of age) as per Table 10. A positive dipstick test would require a serum sample to be sent to the central laboratory for confirmation. Pregnancy test dipsticks will be provided to the sites before study initiation. Details on pregnancy testing requirements are located in Appendix 6.

7.3.8 Clinical Laboratory Evaluations

A designated laboratory (or laboratories) will perform the analyses of all specimens collected. Collection, shipment of samples, and reporting of results by the central or local (if needed) laboratory (or laboratories) will be detailed in the laboratory manual provided to the Investigators. Collection for local labs should be performed for all subjects at screening. If the age/weight of the subject permits, collection for central labs should also be performed at screening, in addition, in order to facilitate comparison of later samples sent to the central lab. If age/weight of the subject does not allow for this additional blood volume, then local labs at screening will serve as baseline labs. The laboratory tests to be performed for subjects in this study are listed in Table 12.

If necessary, laboratory assessments may be performed by a laboratory other than the designated laboratory. In this case, normal ranges of test values for this laboratory should be provided to the Sponsor.

The Investigator at each site is required to review all clinically relevant laboratory results requested in the protocol and to record those results in the CRF. The diagnosis associated with any clinically significant laboratory abnormalities should be recorded as an AE on the CRF. The reported AE should indicate the underlying abnormality or diagnosis (e.g., renal insufficiency) as opposed to the observed deviation in laboratory results (e.g., elevated creatinine) if in fact the underlying abnormality or diagnosis is known. If there is no apparent underlying abnormality

linked to a clinically significant abnormal laboratory value, the observed deviation itself should be reported as the AE.

Table 12: Laboratory Tests†

Chemistry	Hematology	Urinalysis
Albumin	Basophils	Blood
Alkaline phosphatase (AP)	Eosinophils	Glucose
ALT (SGPT)	Hematocrit	Ketones
AST (SGOT)	Hemoglobin	Microscopic exam
Bicarbonate	Lymphocytes	pH
Blood urea nitrogen (BUN)	Monocytes	Protein
Calcium	Neutrophils	Specific gravity
Chloride	Platelets	Bilirubin
Creatinine	RBC	Urine pregnancy test*
Direct Bilirubin	Total WBC	
Glucose	MCV	
Inorganic phosphorus	MCHC	
LDH	MCH	
Potassium	MPV	
Serum pregnancy test (beta hCG)*	RDW	
Sodium	PTT/INR	
Total Bilirubin	**Special**	**Lipid Panel**
Total protein	HIV-1‡	Total cholesterol
GGT	HIV-2‡	HDL
CPK	HBsAg‡	LDL
hsCRP	Anti-HBsAg‡	Triglycerides
	Anti-HBcAb‡	
	Anti-HCV‡	
	CMV	
	ESR (local only)	
	[redacted]	

† Collection for local labs should be performed for all subjects at screening. If the age/weight of the subject permits, collection for central labs should also be performed at screening, in addition, in order to facilitate comparison of later samples sent to the central lab.

‡ If HIV and/or hepatitis testing was performed within 3 months of screening, the results from these tests may be used, instead. The determination of active hepatitis B or C is at the discretion of the Investigator.

* A serum pregnancy test is required at Screening for all females of childbearing potential (≥10 years of age). Post screening, a urine dipstick pregnancy test will be performed on all females with childbearing potential (≥10 years of age) at Day 56, Day 100 and for Unscheduled Visits.

7.3.9 Assessment of Ectopic Tissue Formation (optional per Investigator's discretion)

To detect any ectopic tissue formation, a radiologist and an Investigator at each study site will compare the CT/MRI scan, if collected at screening, with the CT/MRI scan performed at study end to determine if there is ectopic tissue formation. The same method of radiologic scan should be used for both evaluations. If the formation of ectopic tissue is suspected, further evaluation may be indicated, which could include positron-emission tomography (PET) scanning and possibly biopsy.

With consideration of the low incidence of ectopic tissue formation from the safety data, the risk of high radiation exposure from computed tomography (CT) scans, the required administration of contrast agents, and the potential need for anesthetics in an ailing pediatric subject population, **Investigators may choose to omit CT/MRI scans at their own discretion, provided the rationale for omission is documented in the source documents.**

7.4 Long-Term Safety and Efficacy Follow-Up

Long-term efficacy and safety assessments will be performed at Days 56 and 100. At Day 56 (±2 days), a GVHD and remestemcel-L therapy assessment will be performed to determine whether subjects show response to Continued and/or Flare Therapy, when applicable. At Day 100 (±7 days), assessments of GVHD grade and survival will be determined.

In addition, an extension study under a separate protocol (MSB-GVH002), subsequent to the present study, is also planned in order to capture health outcomes and safety data out to Day 180.

7.5 Missing or Delayed Study Visits

Every effort should be made to ensure compliance with prescribed study visits. Missing of study visits is generally not permitted. However, in exceptional situations and with the Sponsor's approval, visits may be postponed.

7.6 Subject Demographics and Other Baseline Characteristics

Demographic data will include:

- Gender
- Age
- Race and ethnicity
- Smoking Status (Never Smoked, Current Smoker, Previous Smoker)
- Weight

- Height
- Body mass index (BMI).

The baseline characteristics will include:

- Subject's medical history and medications related to GVHD
- General medical history, physical examinations, vital signs
- Donor compatibility
- HSCT source
- Grade of aGVHD at onset
- Grade of aGVHD at baseline.

7.7 Monitoring after Administration of IMP

A schedule of clinical assessments is provided in Table 13. All clinical assessments should begin -15 ± 5 minutes prior to IMP administration, at the start of IMP administration (Time = 0) and then 15 ± 5 minutes, 30 ± 5 minutes, 60 ± 5 minutes, and 120 ± 5 minutes after the start of IMP administration.

Table 13: Monitoring Procedures During and After Administration of IMP

	Prior to Administration of IMP	IMP Administration	Time During/After Start of Administration of IMP			
	-15 ± 5 minutes	Time 0 (start of IMP administration)	15 ± 5 min.	30± 5 min.	60 ± 5 min.	120 ± 5 min.
IV Infusion of Treatment		X				
Heart rate (beats/min.)	X	X	X	X	X	X
Systolic/Diastolic Blood pressure (mmHg)	X	X	X	X	X	X
Temperature (°C/°F)	X	X	X	X	X	X
Respiratory rate (breaths/min.)	X	X	X	X	X	X
Oxygen saturation (%)	X	X	X	X	X	X

7.8 Background, First-Line, Second-Line, and Concomitant Medication

If an agent used for prophylaxis of aGVHD is discontinued and restarted prior to initiation of corticosteroids to treat aGVHD, it is considered a prophylactic agent. If the agent is restarted after initiation of corticosteroids to treat aGVHD, it would be considered a second-line agent.

7.9 Concomitant Medication and Supportive Therapy

Information on all concomitant medications will be collected for this study, including information on all concomitant therapy to treat aGVHD.

7.9.1 Standard of Care for aGVHD

All enrolled subjects will receive institutionally defined standard of care (i.e., maintenance of steroid treatment and other prophylactic treatment for aGVHD). In addition, investigators should provide standard of care for prevention and treatment of viral infections, particularly if there is evidence of viral reactivation. In some cases, such as those involving adenoviral treatment or where no other approved treatment is available, patients may be treated with experimental agents at the Investigator's discretion. However, if a subject begins other second-line therapy for GVHD (e.g., anti-TNF or anti-IL-6 agents) within the period of Initial and Continued Therapy (through Day 56, if applicable), he or she would be considered to have failed treatment and would be ineligible to receive any further remestemcel-L therapy upon receiving the other second-line GVHD therapy.

7.9.2 Concomitant Medications

Information on all concomitant medications will be collected for this study, including information on all concomitant therapy to treat aGVHD.

Subjects may continue to be treated with a stable dose of systemic steroid therapy until subject is able to be tapered following initiation of remestemcel-L (Day 0). Subjects may also continue any prior therapy used for prophylaxis at a stable regimen from baseline. No other GVHD medications are to be introduced to subjects during the initial 28 days post remestemcel-L administration unless disease has progressed.

If a subject begins other second-line GVHD therapy within the period of Initial and Continued Therapy (through Day 56, if applicable), he or she would be considered to have failed treatment and would be ineligible to receive any further remestemcel-L therapy upon receiving the other

second-line GVHD therapy. However these subjects would remain on the study for safety follow up.

Second line agents to treat GVHD will be coded using the World Health Organization dictionary (latest available version) and presented by preferred term for GVHD second line agents based on reported drugs for GVHD treatment.

7.9.3 Steroid Taper

If improvement in GVHD (CR or PR) is observed for a period of 3-5 days and after at least two doses of remestemcel-L, the dosing of methylprednisolone or equivalent may be tapered. A steroid taper rate of at least 10% of the dose per week but not to exceed 25% of the dose per week is recommended as described in Appendix 5, with the goal of discontinuing steroid by 10 weeks after initiating taper.

7.9.4 Escalating of Steroid Therapy

Protocol guidelines for escalating steroid therapy of aGVHD for worsening disease include:

1. Worsening of symptoms for at least 3 days OR
2. Grades C-D aGVHD persisting for at least 1 week despite treatment OR
3. Grade B aGVHD persisting for at least 2 weeks despite treatment.

Escalation of steroid therapy prior to Day 28 does not constitute withdrawal of a subject from the study. If escalation of steroid therapy occurs, the subject is to continue on the study and receive all treatments and assessments per protocol. If second line agents are added, the subject would remain on study for safety follow up and would not receive any further remestemcel-L treatment.

7.9.5 Supportive Care

In addition to prescribed investigational agent plus corticosteroids and prophylactic therapies, all subjects may receive the following:

- Transfusion support per institutional practice. Type of transfusion and the number of units will be recorded in the eCRF.
- Anti-infective prophylaxis directed towards: CMV, gram positive (encapsulated) bacteria, pneumocystis carinii and fungal infections per institutional practice.

[redacted]

8. SAFETY GUIDANCE

8.1 Definitions

8.1.1 Adverse Event

An AE is defined by the International Conference of Harmonization (ICH) guideline for Good Clinical Practice as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.

Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening procedures such as biopsies etc.) are to be reported.

Recording of AEs will begin upon signing of the informed consent form (ICF). Pre-existing conditions that **worsen** during a study are to be reported as AEs.

8.1.2 Serious Adverse Event (SAE) (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the Investigator, places the subject at immediate risk of death)
    - This does not include any AE that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

8.1.3 Severity

A clinical determination will be made of the severity of an AE. The terms "severe" and "serious" are not synonymous. Severity is a description of the intensity of the manifestation of the AE and is distinct from seriousness, which implies a subject outcome. Severity will be assessed according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale. [63] (Table 14)

Table 14: NIH Common Criteria for Adverse Events (CTCAE) Scale †

AE Severity	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening; urgent intervention indicated.
Grade 5	Death related to AE

† Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. National Cancer Institute. US Department of Health and Human Services. June 14, 2010. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
*Instrumental activities of daily living (ADL) examples include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL includes to bathing, dressing and undressing, feeding self, using the toilet, and taking medications and does not include being bedridden.

8.2 Relationship of Adverse Event to the IMP

A determination will be made of the relationship between an AE and the IMP. A causal relationship is present if a determination is made that there is a *reasonable possibility* that the AE may have been caused by the IMP. In general, a causal relationship will be assigned when evidence exists to support the causal relationship.

When assessing a potential relationship between the IMP and an AE, the following parameters should be considered:

- Temporal relationship between IMP and/or protocol-specified procedures and the AE.
- The biological plausibility that the IMP caused the event
- Any underlying/concurrent illness in the subject
- Concomitant medications the subject may have received
- How commonly the event occurs in the study population independent of treatment.

8.3 Relationship to Study Procedure

For each AE, the relationship to the IMP delivery procedure must be recorded as either **related** (there is a reasonable possibility of a causal relationship between the event and the study procedure) or **not related** (there is not a reasonable possibility of a causal relationship between the event and the study procedure).

9. REPORTING ADVERSE EVENTS

9.1 Procedures for Reporting Adverse Events and Serious Adverse Events

Any AE occurring after a subject has signed the informed consent should be recorded on the appropriate CRF page.

Any SAE (as described in Section 8.1.2) occurring after a subject has signed the informed consent should be immediately reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the event. All subjects with an SAE must be followed up and the outcomes reported until the event is resolved or has stabilized.

Upon occurrence of an SAE, the Investigator must:

- Immediately notify the Sponsor's designee, Quintiles Lifecycle Safety (QLS). SAE reporting will originate in the electronic data capture (EDC) system and an email will be sent to individuals with designated responsibility for safety. Primary and secondary cause(s) of death will be recorded on the eCRFs for SAEs that are fatal.
- The paper SAE form is in place as a back-up in the rare event that EDC is not accessible to the reporter of the SAE:
    - If the EDC is not available, email the SAE form to the QLS safety mailbox: [redacted]
- Provide copy of all relevant source documents, including medical history, and concomitant medications, as appropriate.

All SAEs that are considered unexpected and related to the study product will be reported by the Sponsor or its designee as a 15-day report to the Regulatory Authorities *as applicable* and to all participating investigators.

SAEs that are considered unexpected, related to the study and are life threatening, or result in death will be reported by the Sponsor or its designee to the appropriate Regulatory Authorities and to all participating investigators as a 7-day report.

Each investigator must notify the IRB/EC responsible for reviewing the study at their site of all 15-day or 7-day safety reports required by local regulations or IRB/EC requirements and shall provide the Sponsor or its designee with written confirmation of said IRB/EC notification.

9.2 24-Hour Urgent Medical Contact

A Quintiles Medical Advisor is available for 24/7 urgent contact in this study. If the Quintiles Medical Advisor is not able to provide 24/7 services for a period longer than 2 hours (e.g. for international business travel) or during vacations, adequate medical back-up with documented training on the protocol and experience with the therapeutic area will be arranged and communicated. The system of 24/7 coverage ensures that a qualified medical advisor is available for advice within a safe and reasonable time frame.

The following additional numbers are also available for 24/7 urgent contact:

[redacted] **or** [redacted]

9.3 Procedures for Reporting Pregnancies

All pregnancies that occur during the study are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the Investigator must provide Sponsor or designee, by facsimile, a Pregnancy Tracking Form. Pregnancies in female partners of male subjects are **not** required to be followed up. All subjects who become pregnant will be monitored to the completion or termination of the pregnancy, including perinatal and neonatal outcome. Monitoring of the subject should continue until conclusion of the pregnancy. If the pregnancy is associated with an SAE (e.g. hemorrhage, spontaneous abortion), in addition to the Pregnancy Form, a separate SAE form must be provided as described in Section 9.

9.4 Laboratory Test Abnormalities

Laboratory test results will appear on laboratory reports that are submitted directly from the central laboratory. Local laboratory results should be recorded on the CRF, if applicable.

Any laboratory result that fulfills the criteria for an SAE should be reported as both an SAE and as an AE in the CRF.

Any treatment-emergent abnormal laboratory result that is clinically significant should be recorded as a single diagnosis in the CRF. A treatment-emergent abnormal laboratory result is considered to be clinically significant if it meets one or more of the following conditions:

- Is accompanied by clinical symptoms.
- Requires change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

These conditions will apply to any protocol- and non-protocol- specified safety and efficacy laboratory results from tests performed after ICF signature that fall outside the laboratory reference range and are considered clinically significant. These conditions will not apply to any abnormal laboratory results that are outside the laboratory reference range, yet does not meet the criteria for clinical significance; these latter results will be analyzed and reported as laboratory abnormalities.

In the event of clinically significant abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or the abnormality is adequately explained or accounted for. If an acceptable explanation is established, it should be recorded on the CRF.

9.5 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

The Sponsor will promptly evaluate all AEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- IMP IB
- IMP Development Core Safety Information (DCSI) Document, if applicable.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

10.1 Study Design and Randomization

This is an open-label single-arm study. No randomization will take place. All enrolled subjects will be treated with remestemcel-L.

10.1.1 Sample Size and Power

The primary objective of this trial is to confirm efficacy of remestemcel-L in improving Day 28 OR rate within the full analysis set (FAS) population. [6]

For assessment of efficacy, an effect size of 20%, which has been deemed clinically meaningful based on discussions with clinical experts on aGVHD, was used to calculate the null hypothesis. The null hypothesis was calculated using 45% OR, a rate that is 20-points lower than the anticipated 65% OR rate to remestemcel-L. This estimated 45% response rate as the null hypothesis is further supported by data showing comparable Day 28 OR rates for historical populations of aGVHD patients treated with standard of care. [6,16]

[redacted]

In this study, a 28-day OR rate for a subject population treated only with steroids was conservatively anticipated to be 65%, [redacted] Hence, p=0.65 was chosen as the alternative hypothesis.

Accordingly, the null and alternative hypotheses are as follows:
H_0: p = 0.45 vs. H_a: p ≠ 0.45

Sample size was determined using the East 6.0 software. The hypothesis test uses a normal approximation to the binomial distribution under the assumption of a symmetric two-sided one-

sample test of the significant level 5% for a single proportion. Sample sizes for power fixed at 80% and at different choices of the alternative are displayed in Table 15.

Table 15: Sample Size Consideration

P in Alternative Hypothesis	Sample Size
0.60	86
0.64	53
0.65	48
0.70	30
0.75	20
0.781	16
0.80	15
0.818	13
0.85	11

Thus, the minimum sample size required to meet the primary objective with 80% power is 48 for the FAS population. At least 48 subjects will be enrolled. In order to account for dropouts/missing data and to ensure that this study has sufficient power, an additional increased enrollment of up to 10% of the minimum required enrollment (48) is planned.

10.1.2 Sample Size for Interim Analysis of Futility

The present trial may be stopped as a result of an interim analysis for futility.

The interim analysis is planned after approximately 30 subjects treated with IMP are assessed for 28-day OR. At this interim, the trial may declare futility or continue to completion. The decision rules for futility are described below.

10.1.3 Interim Analysis of Futility

The trial may be stopped for futility as a result of one interim analysis. The actual boundary used will depend on the number of subjects who completed the 28-day follow-up at the point at which the Interim Analysis is actually conducted. The preferred time point is midway into the study, which is the point at which approximately 30 subjects is expected to have completed the 28-day follow-up; if the exact 30-subject point is not used, then the boundary based on the number of subjects in the study will be used. Details will be specified in the SAP for the study and in the DSMB charter.

10.2 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be prepared prior to Database Lock (DBL) containing details of the statistical analyses and data-handling rules planned for this trial. Post-DBL changes to the SAP will be documented in the Clinical Study Report. An overview of main methods is given below.

10.2.1 General Statistical Considerations:

Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Confidence intervals, if presented, will have a 95% confidence level.

The baseline value for a variable is defined as the last non-missing observation taken prior to or on the first dose date of study treatment. By this definition of baseline, post-baseline is defined as data collected after first infusion (complete or partial) of study treatment. Data collected at unscheduled time points will not be summarized at the unscheduled time points, but will be considered as for baseline.

The first dose date will be considered the 'Study Day 0'. The study day, the actual day relative to start of treatment, will be calculated from Study Day 0.

The primary efficacy analysis will be based on the FAS population. Analyses of the mFAS and PP populations will be used to assess sensitivity and thus will be considered supportive.

All statistical tests will be two-sided at the alpha=0.05 level of significance. Confidence Intervals will be two sided at the 95% level.

10.3 Analysis Populations

10.3.1 Full Analysis Set (FAS)

This is a single-arm study with no randomization after screening. All subjects who provided informed consent, were screened and found eligible to enter the study will belong to the FAS population. The FAS will be used for the primary efficacy analysis. Secondary efficacy analyses will also be performed on the FAS population.

10.3.2 Modified Full Analysis Set (mFAS)

The mFAS is all subjects who provided informed consent, were screened and found eligible to enter the study, however, were treated with IMP stored in cryogenic vials. Primary and secondary efficacy analyses will also be performed on the mFAS population.

10.3.3 Safety Population

The safety population will include all FAS subjects who receive at least one dose of study treatment (complete or partial).

10.3.4 Per-Protocol (PP) Population

The per-protocol (PP) population will include all subjects who had no major protocol violations during the study. In general, not meeting inclusion criteria or meeting any exclusion criteria would be assessed as major protocol violations.

The primary efficacy analysis will be repeated as a sensitivity analysis on the mFAS and PP populations. The key secondary efficacy analyses will be repeated for the mFAS and PP populations for Overall Survival at Day 100 post initiation of remestemcel-L therapy. The primary and secondary efficacy analyses performed on the mFAS and PP populations will be considered supportive.

10.4 Demographic and Baseline Characteristics

Pre-treatment demographics and subject characteristics will be summarized. Descriptive statistics [e.g., number of subjects, mean, standard deviation (SD), median, minimum, and maximum] will be calculated for continuous variables [e.g. age and weight] and frequency counts will be tabulated for categorical demographic variables [e.g. gender, ethnicity, race, underlying malignancy or leukemic disease at transplant, donor type, donor compatibility, HSCT source, grade of aGVHD at onset, grade of aGVHD at baseline]. Time from HSCT to onset of aGVHD and onset of aGVHD to initiation of study drug will be summarized. Involvement of the skin, lower gastrointestinal (GI) tract, and liver will be summarized by the number of subjects with one organ, two organs, or all three organs involved at baseline.

10.5 Efficacy Analysis

10.5.1 Primary Efficacy Endpoint

Overall Response (OR) at Day 28

OR at Day 28 to remestemcel-L treatment is the primary efficacy endpoint. If a subject dies before Day 28 or if additional second-line treatment was required before Day 28, then the Day 28 response will considered "No Response" regardless of the actual response reported on the Day 28 assessment form or the end-of-trial form. For subjects enrolled but not treated, the Day 28 response will also be considered "No Response". If a subject needs to withdraw from the study because of an SAE or because of need for palliative care due to a lack of GVHD response and has completed a 28 day end point assessment, the data from the 28-day assessment will be used.

Missing data for the primary endpoint will be imputed non-responders. No other imputation is planned, as specified in the SAP.

A hypothesis test will be performed to assess whether the percentage of responders is statistically significantly different from the historical control percentage of 45%.

10.5.2 Secondary Efficacy Endpoints

10.5.2.1 Overall Survival at Day 100 post initiation of remestemcel-L therapy

Survival will be assessed from initial remestemcel-L treatment to the last date of assessment. Since the trial period is 100 days, survival information will be censored at the 100 day time point.

Data-handling rules taking account of visit windows for ascertaining survivor/non-survivor status at Day 100 will be detailed in the Statistical Analysis Plan (SAP).

Percentages of survivors and deaths will be based on all subjects, including those with missing survival information for the lost to follow-up or withdrawal.

The association between Day 28 OR and survival at Day 100, and between Day 28 VGPR and survival at Day 100, will be tested for statistical significance. First, the associations will be tested using a Cochran-Mantel-Haenszel (CMH) test, stratifying by baseline aGVHD grade. Day 100 survival Kaplan-Meier curves will be plotted by Day 28 responder and non-responder groups, and differences between these groups will be tested for a statistically significant

difference using the log-rank test. The odds ratio for survival at Day 100 given responder status at Day 28 will be presented and tested for statistical significance (whether statistically significantly greater than 1).

10.5.2.2 Rate of Very Good Partial Response (VGPR) at Day 28 post initiation of remestemcel-L therapy

The rate of VGPR, defined in Table 4, will be described. The number and proportion of VGPR responders, non-responders, and missing values, will be summarized. The two sided 95% confidence intervals will be presented for these estimates.

10.5.2.3 Rates of OR and VGPR at Day 100 post initiation of remestemcel-L therapy

The number and percentage of responders at Day 100 and for each endpoint will be summarized. Confidence Intervals at the 95% level (two sided) will be presented for estimates of proportions.

10.5.2.4 Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy stratified by organ involvement

The rates of OR and VGPR at Day 28 and at Day 100 will be reported by skin, gut (lower GI), or liver involvement at baseline. Confidence Intervals at the 95% level (two sided) will be presented for estimates of proportions.

10.5.2.5 Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy stratified by individual subject organ involvement

The rates of OR and VGPR at Day 28 and Day 100 will be reported by the mutually exclusive Skin-only and "Not skin-only" categories. Confidence intervals at the 95% level (two sided) will be presented for estimates of proportions.

10.5.2.6 Rates of OR and VGPR at Days 28 and 100 post initiation of remestemcel-L therapy stratified by baseline aGVHD grade

The number and percentage of responders at each time point and for each endpoint will be summarized by baseline GVHD grade. Two-sided confidence intervals at the 95% level will be presented for estimates of proportions.

10.5.2.7 Overall survival at Day 100 post initiation of remestemcel-L therapy stratified by baseline aGVHD grade and organ involvement

The number and percentage of survivors at Day 100 from first infusion date will be summarized by baseline grade and organ involvement. Confidence Intervals at the 95% level (two sided) will be presented for estimates of proportions.

10.5.2.8 Rate of aGVHD progression requiring additional GVHD medications/ therapy through Day 100 post initiation of remestemcel-L therapy

The incidence rate of GVHD progression requiring additional GVHD medications or therapy will be summarized by number and proportion of subjects. Two-sided confidence intervals at the 95% level will be presented for estimates of proportions.

10.5.2.9 Effect of additional remestemcel-L therapy after Day 28 on rate of OR and VGPR at Days 56 and 100 post initiation of remestemcel-L therapy

Side-by-side shift tables, for response at Day 56 and response at Day 100 versus response at Day 28, summarizing the effect of additional IMP therapy, will be presented.

Efficacy analyses will include a summary of aGVHD grade at baseline, Day 28, Day 56 and Day 100. Shift tables in aGVHD organ stages from baseline to Day 28 will be presented. Shift tables for organ stages will also be presented by organ involvement. Shift tables will also be presented for skin-only stages and separately for “All Others” (that is, excluding skin-only). Response by organ for each of these groups (by individual organ involvement, skin-only and all-others) will also be summarized as improving, stable or progressing, together with the number of deaths in each case.

As sensitivity analyses, survival will also be calculated from the day of transplant and from the day of diagnosis of aGVHD to the last date of contact. For all survival data, Kaplan-Meier survival curves will be generated and relevant subgroups will be compared using the log-rank test. Kaplan-Meier curves will also be generated by number of organs involved, and by number of infusions (categorized).

[redacted]

10.6 Safety Data Analysis

10.6.1 Primary Safety Endpoints

The primary safety parameters to be assessed include:

1. Adverse events
2. Serious adverse events
3. Infusional toxicity
4. Formation of ectopic tissue foci.

Safety analyses will be performed in a descriptive fashion using the Safety population.

10.6.2 Adverse Events and Serious Adverse Events

All AEs will be collected in this study and summarized by treatment, dose, and severity. Numbers and rates of TEAEs and other safety variables will be tabulated by organ system and preferred term.

Serious adverse events, grouped by organ system and preferred term, will be summarized. Details on how AEs/SAEs will be presented will be outlined in the SAP.

10.6.3 Infusional Toxicity

The number and percent of subjects with infusional toxicity will be summarized by System Organ Class (SOC), High Level Term (HLT), and Preferred Term (PT) based on the SAE report form with PT of infusion related reaction as designated by the Investigator. AEs which are infusional toxicity events will be summarized.

10.6.4 Other Safety Analyses

10.6.4.1 Study Drug Exposure

The total number of study drug infusions that subjects received and the extent of exposure will be summarized with descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). The number of subjects receiving fewer or greater than 8 study drug infusions will be summarized.

10.6.4.2 Survival

The number of subjects alive, dead, and lost to follow-up or withdrawal will be summarized in a Subject Disposition table. For subjects who died, the time to event will be calculated from date of transplant, date of aGVHD onset, and date of treatment initiation. All other subjects will be censored, and survival time will be calculated, from the date of transplant, date of aGVHD onset, or date of treatment initiation, to the date of last contact.

10.6.4.3 Handling of Missing Values

Missing data for the primary endpoint will be treated as non-responders. Details regarding the handling of missing values for all other endpoints will be detailed in the MSB-GVHD001 Statistical Analysis Plan (SAP).

10.6.4.4 Subgroups

[redacted]

11. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Sponsor's (or designee's) Standard Operational Procedures (SOPs).

Data for this study will be recorded using the Medidata Rave System and eCRF.

The site is expected to respond to all SAE queries within 24 hours and all others within 5 business days. A Mesoblast representative, or a designee, will perform final data review and external data reconciliations prior to all major milestones, including database close and lock.

11.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) [64] terminology for AEs and diseases and for treatments and surgical and medical procedures.

12. STUDY COMMITTEES

12.1 Independent Data and Safety Monitoring Board (DSMB)

A data and safety monitoring board (DSMB) will be set up for the trial to oversee the management of the trial, review the overall safety data, and propose appropriate actions if necessary. The independent DSMB will consist of physicians with expertise in oncology, stem cell transplantation, and conduct of clinical trials and an independent biostatistician. The composition of the DSMB and its specific working procedures will be described in a separate charter. This charter will clearly specify attendees, rules and responsibilities, procedures, review meeting schedule and the data to be analyzed.

The DSMB will follow the DSMB charter and data analyses will be done according to the DSMB charter.

In addition to the regular monitoring of safety, one interim analysis is planned for this study as described in Section 10.1.3. The DSMB will review the data for futility and may make a recommendation on whether to stop the trial for futility, as a result of this interim analysis.

[redacted]

12.2.2 Follow-up of Safety and Health Outcomes

An extension study (MSB-GVHD002), subsequent to the present study, under a separate protocol is being conducted in order to capture health outcomes and safety data out to Day 180. Subjects may be presented with the IRB/EC approved consents for MSB-GVHD001 and MSB-GVHD002 simultaneously at the time of consent onto this protocol.

13. LAWS, REGULATIONS, AND ETHICS

13.1 Local Regulations/Declaration of Helsinki

This clinical study shall be conducted in full compliance with current material and relevant laws and regulations and the Investigator will use best efforts to ensure such compliance. This clinical study will also be conducted in compliance with principles outlined in the "Guideline for Good Clinical Practices" ICH tripartite Guideline [70] and with the ethical principles of the "Declaration of Helsinki" [71] or with the laws and regulations of the country in which the research is conducted, including but not limited to the EU Clinical Trial Directive. [72]

13.2 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator, if local regulations permit, to obtain signed Informed Consent from each subject prior to the subject's participation in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For subjects who are not qualified to or are incapable of giving legal consent, written consent must be obtained from a legally acceptable representative. In cases where both the subject and his/her legal representative are unable to read, an impartial witness must be present during the entire Informed Consent discussion. After the subject and representative have orally consented to participation in the trial, the witness' signature on the form would attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that subjects are free to refuse to enter or withdraw from the study at any time and for any reason, that a copy of the consent would be provided to the subject, and that the process by which consent is obtained is described in the source documentation. The CRFs for this study would contain a section for documenting subject informed consent, which must be completed appropriately. If new safety information results in significant changes in the benefit/risk assessment, the consent form should be reviewed and updated if necessary. All subjects, including those already being treated, should be informed of the new information, provided with a copy of the revised form, and give their consent to continue in the study in accordance with the IRB/EC requirements.

13.3 Institutional Review Board/ Ethics Committees (IRB/EC)

This protocol and any modifications as well as appropriate consent procedures, any accompanying material provided to the subject, such as subject information sheets or descriptions of the study used to obtain informed consent, and advertisements or compensation given to the subject, will be reviewed and approved by an appropriate competent authority and IRBs/ECs.

Before initiation of the trial at each investigational site, approval from the appropriate IRB/EC must be obtained. Written approval must be obtained before a trial site is initiated or the investigational product is released to the Investigator.

Any extensions or renewals of IRB/EC approval must be obtained during the course of the study. If required, approvals must also be obtained for any changes to the protocol, the Informed Consent form, the written information provided to subjects, and/or other procedures.

Any new information that may adversely affect the safety of the subjects or the conduct of the study will be reported promptly to the IRB/EC by the Investigator and/or the Sponsor, in accordance with applicable local requirements. Written summaries of the study status will be submitted to the IRB/EC annually, or more frequently if required by the EC/IRB. On completion of the study, the IRB/EC will be notified that the study has ended.

13.4 Protocol Adherence

Investigators will ensure that due diligence is applied in order to avoid protocol deviations or violations as defined below. All significant protocol deviations and violations will be reported to the IRB/EC in accordance with IRB/EC requirements. All significant protocol deviations and violations will be recorded and reported in the CSR.

13.5 Protocol Deviation

A protocol deviation is defined as an intentional or unintentional change or non-compliance with a research protocol.

14. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from investigators to modify the protocol for ongoing studies will be considered only by consultation between an appropriate representative of the Sponsor and the Investigator. Protocol modifications must be prepared by a representative of the Sponsor and approved by the Sponsor.

All protocol modifications must be submitted to the appropriate IRB/EC for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor[s], change of telephone number[s]).

15. CONDITIONS FOR TERMINATING THE STUDY

Mesoblast reserves the right to terminate the study at any time under the conditions specified in the Clinical Trial Agreement. In the event the trial is terminated before the planned completion date, action will be taken to assure the protection of the subjects' interests.

15.1 Enrollment Hold and Stopping Rules

Subject safety will be continuously monitored. The Investigator site will report all SAEs, including all deaths immediately as outlined in Section 9.

Additionally, all AEs including all deaths will be periodically reported to the DSMB as per the DSMB charter. The DSMB will investigate these complications through a complete safety review. The DSMB will investigate futility data during interim analysis review. The DSMB will then determine whether enrollment should be continued, continued with modification, suspended, or terminated, and their decision will be communicated to the Sponsor. Please refer to Section 10.1.3 and the SAP.

16. STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

16.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories, consisting of: 1) An Investigator's Study File and 2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments and schedule of assessments, IRB/EC and governmental approval with correspondence, sample Informed Consent, drug records, staff curriculum vitae, authorization forms, and other appropriate documents/correspondence. In addition, at the end of the study the Investigator will receive the subject data, including an audit trail containing a complete record of all changes to data, query resolution correspondence, and reasons for changes, in a readable format on CD that must be kept with the Investigator’s Study File.

Subject clinical source documents may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, special assessment reports, signed informed consent forms, and consultant letters. The Investigator must keep the Investigator’s Study File and subject clinical source documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study, or in accordance with ICH guidelines and local regulations, whichever is of greater duration. After this specified time period, the documents may be destroyed. Study sites must notify the Sponsor prior to destroying any trial-related documents.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee compliance with this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these documents in a sealed container(s) outside of the site in order to ensure that they can be returned sealed to the Investigator in the event of a regulatory audit. Where source documents are required for continued care of subjects, appropriate copies should be made for storing outside of the site.

16.2 Source Documents and Background Data

The Investigator shall provide to the Sponsor, upon request, any required background data from the study documentation or clinic records. This is particularly important in cases where errors in data transcription are suspected. In cases of special problems and/or governmental queries or requests for audit inspections, it is also necessary for the Sponsor to have direct access to the complete study records, provided that subject confidentiality is protected.

16.3 Audits and Inspections

Source documents for this trial must be made available by the Investigator to appropriately qualified personnel from the Sponsor's (or designee's) Quality Assurance Unit or its designees or to health authority inspectors, upon appropriate notification. Verification of the CRF data must be by direct inspection of source documents.

16.4 Electronic Case Report Forms

Data for this study will be captured via an Electronic Data Capture (EDC) system by using eCRFs. The data will be entered into the EDC system by trained site personnel per the eCRF Completion Guidelines. An audit trail will maintain a record of initial entries and changes made, reasons for change, time and date of entry, and user name of person authorizing entry or change.

An eCRF must be completed for each enrolled subject. For each screen-failed subject, the reason for screen failure will be collected in the Completion eCRF along with the corresponding screen failure reason. The entire subject casebook of data must be reviewed and electronically signed by the Investigator or by an authorized delegate from the study staff. This also applies to records for those enrolled subjects who fail to complete the study. If a subject withdraws early from the study, the reason must be noted at the end of the study eCRF. If a subject is withdrawn

from the study because of a treatment-limiting AE, attempts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

17. MONITORING OF STUDY

The Sponsor's responsible monitor (or designee) will contact and visit the Investigator regularly and will be permitted, upon request, to inspect the trial records, including CRFs and other pertinent data, provided that subject confidentiality is maintained in accordance with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to ensure protocol adherence and that the data entered on the CRFs are complete, consistent, and accurate. The monitor must verify that the subject received the study drug. The monitor will also have access to laboratory test reports and other subject records as applicable needed to verify entries on the CRFs. The Investigator (or deputy) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

18. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must ensure that subject anonymity is maintained and that subject identity is protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, subjects should be referenced by an identification code rather than by their names. The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator should maintain documents that will not be submitted to the Sponsor (e.g., subjects' written consent forms) in strict confidence.

19. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

19.1 Right to Publish

Subject to the restrictions in this Article 18 and processes described in this Section 19, an Investigator may individually communicate, orally present, or publish in scientific journals or other scholarly media, the study results. The Sponsor retains the title and all rights to, as well as interest in, the study data and case report forms. Authorship will be determined by mutual

agreement according to guidelines published by the International Committee of Medical Journal Editors (ICMJE). [73]

19.2 Publication Steering Committee

A Publication Steering Committee (the "Committee") appointed by Sponsor will be responsible for the creation, review and submission of publications and presentations relating to the study (i.e. primary manuscript on design, baseline data, mortality, efficacy and safety data) and sub-study, ancillary analyses after completion of the study. The Committee will encourage and support other manuscript(s) for publication, content for speaking engagements, abstracts of papers, poster presentations, and similar material by the Study Center and/or Investigator, as deemed appropriate by the Committee. Prior approval by the Committee must be obtained before any publication or public display of the Study results, alone or in aggregate.

19.3 Procedure

The Investigator shall provide Sponsor with a written copy of any proposed publication or other disclosure of the Study results, including disclosures at research seminars, lectures and professional meetings and the submission of papers for publication, at least sixty (60) days prior to submission for publication or disclosure so that Sponsor may have a reasonable opportunity to: (i) review and comment on the contents of the proposed publication or disclosure; (ii) identify any trade secrets, proprietary information or Confidential Information (other than the Study results themselves) of Sponsor to be deleted from the proposed publication or disclosure; and (iii) protect proprietary rights to inventions or products developed or investigated under the Study. The Sponsor shall provide, in writing, any comments to the Investigator or identify any of the Sponsor's trade secrets, proprietary information or Confidential Information (other than the Study results themselves) to be edited from the proposed publication or disclosure, within such sixty (60) day period. Upon Sponsor's reasonable request, Investigator shall delay publishing or disclosure for a period not to exceed one hundred twenty (120) days from the date of receipt of such materials by Sponsor to permit the Sponsor to file patent applications or otherwise seek proprietary protection of subject matter disclosed in any proposed publication or other disclosure. In addition, Investigator shall give due regard to Sponsor's legitimate interests, such as manuscript authorship, coordinating and maintaining the proprietary nature of submissions to Regulatory Authorities, and coordinating with other ongoing studies in the same field, and agree to accept Sponsor's reasonable comments and suggestions with respect to such publications or disclosures.

19.4 Multi-Center Study

Investigator and Study Center acknowledge that the Study is part of a multicenter study. Accordingly and notwithstanding anything to the contrary herein, Study Center and/or Investigator shall not publish or present the Study results until after the first publication, primary manuscript, or presentation regarding the overall study is completed, the results of the Study from all the sites have been published in a single publication or eighteen (18) months after acceptance of the manuscript or the conclusion of the Study at all Study sites whichever occurs earliest, the. Thereafter, Study Center and/or Investigator may publish or disclose Study results in accordance with the provisions of this Section 19.

20. STUDY COMPLETION

Mesoblast reserves the right to terminate this protocol prematurely for reasonable cause provided that written notices are submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the protocol at his or her site for reasonable cause, after providing written notice to Mesoblast a reasonable time in advance of the intended termination. Advance notice is not required by either party if the protocol is stopped due to safety concerns. If Mesoblast terminates the protocol for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for termination. If the Investigator elects to terminate the study at his or her site, the Investigator will be responsible for returning all investigational products and study-related documents to the Sponsor in a timely manner. Source documents supporting study-related data must be retained by the Investigator as previously described.

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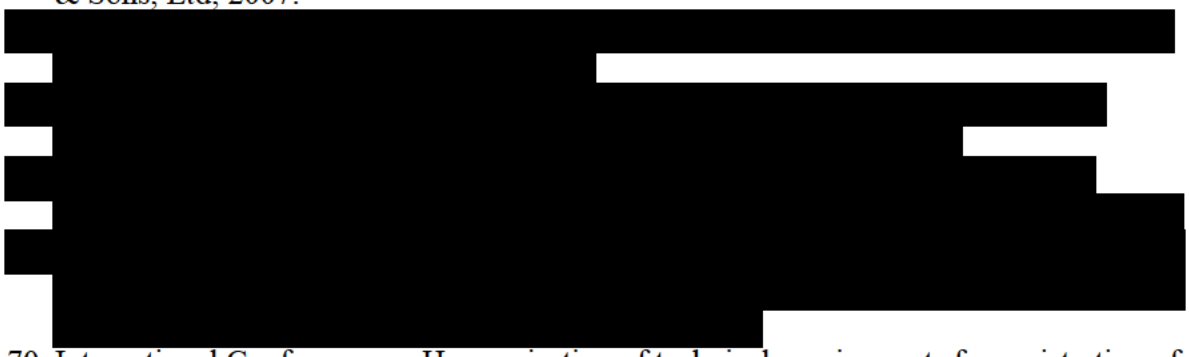

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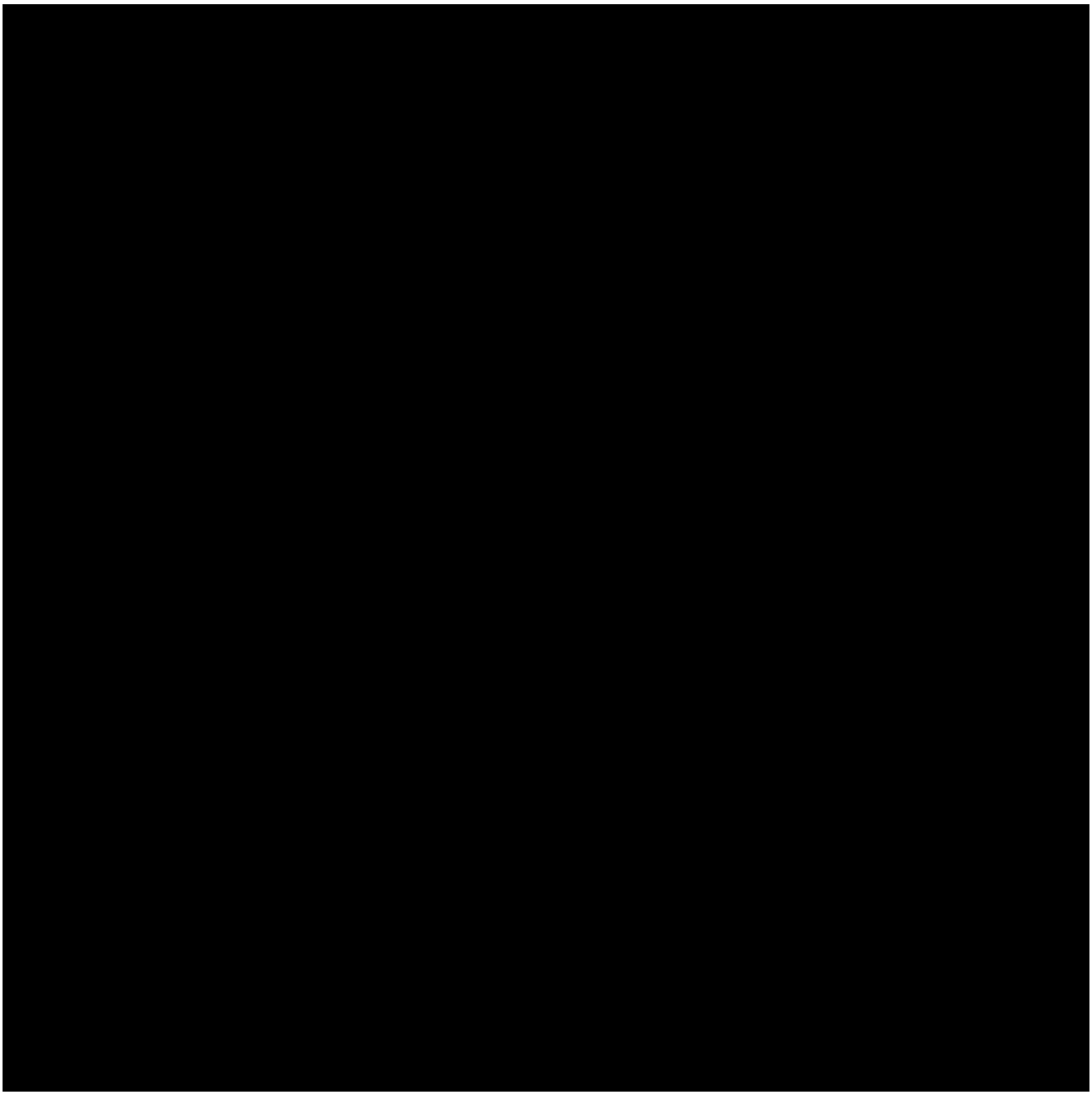

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Appendix 5: Recommended Steroid Taper

Below schemes for steroid tapering is for guidance only. A steroid taper rate of at least 10% of the dose per week, not exceeding 25% reduction of the dose per week is suggested.

Prednisone Orally

2.5 mg/kg/day divided in 2-3 doses	Days 0-6
2.5 mg/kg/day once daily	Days 7-13
2 mg/kg/day	Days 14-21
1.4 mg/kg/day	Days 21-28
0.75 mg/kg/day	Days 29-35
0.6 mg/kg/day	Days 36-42
0.4 mg/kg/day	Days 43-49
0.25 mg/kg/day	Days 50-56
0.1 mg/kg/day	Days 57-63
0.1 mg/kg/every **other day**	Days 63-69
Discontinue	Day 70

Methylprednisolone IV

2 mg/kg/day divided in 2-3 doses	Days 0-6
2 mg/kg/day once daily	Days 7-13
1.5 mg/kg/day	Days 14-21
1.0 mg/kg/day	Days 21-28
0.5 mg/kg/day	Days 29-35
0.4 mg/kg/day	Days 36-42
0.3 mg/kg/day	Days 43-49
0.2 mg/kg/day	Days 50-56
0.1 mg/kg/day	Days 57-63
0.1 mg/kg/every **other day**	Days 63-69
Discontinue	Day 70

Appendix 6: Childbearing Potential, Pregnancy Testing, and Contraception

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at Screening. Post-screening, a urine pregnancy test will be performed at Day 56, Day 100, and at any unscheduled visits under protocol MSB-GVHD001. On protocol MSB-GVHD002, a urine pregnancy test will be performed at End of Study/Day 180 and at any unscheduled visit. If the urine pregnancy test is positive, the result must be confirmed by a serum pregnancy test (conducted by the central laboratory). [1]

All female patients are considered to be of childbearing potential **unless** they meet one of the following criteria:

- The patient has been post-menopausal (amenorrheic) for at least 1 year
- The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to enrollment
- The patient had a hysterectomy.

Female patients of reproductive or childbearing potential who are unwilling to use a highly effective method of contraception for the duration of the study will be excluded from study participation. [2]

Examples of highly effective contraception include the following:

- Abstinence
- Contraceptive pill or transdermal patch
- Single barrier plus spermicide
- Intrauterine device
- Implants for contraception
- Injections for contraception (with prolonged release)
- Hormonal vaginal device
- Sterilization, surgical tubal ligation
- Sole sexual partner consisting of surgically sterilized male partner with appropriate post-surgical verification of the absence of spermatozoa in the ejaculate.

Patients may provide verbal confirmation that the partner completed appropriate follow-up after vasectomy. Sites are not required to obtain partner medical records.

1. Study or protocol-specific.
2. IMP-specific and study-specific.